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THE GEORGE BLUMER
EDITION OF
BILLINGS-FORCHHEIMER'S
THERAPEUSIS OF INTERNAL DISEASES

VOLUME II

THE GEORGE BLUMER
EDITION OF
BILLINGS-FORCHHEIMER'S
THERAPEUSIS
OF INTERNAL DISEASES

CARE AND MANAGEMENT OF MALADIES AND AILMENTS OTHER THAN SURGICAL

Forchheimer, Frederick

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CHAPTER I

PSYCHOTHERAPY

Austen Fox Riggs and William B. Terhune

INTRODUCTION

Psychotherapy, as the term implies, means healing through the medium of the patient's mind. Mental healing is the very oldest form of therapy known. Back in the dark ages before the birth of science, healing was an art and only an art; it was purely suggestive and was applied indiscriminately to all forms of disease and disorder. Nature and all her ways, storms, sunshine, the growing grain, trees bearing fruit, birth, life and death, good and ill fortune, health and disease, all the common phenomena of life must needs have been explained on a supernatural, mystical basis, in the absence of knowledge and that interpretation of facts called science. Hence, illness must have seemed mysterious, perhaps the most mysterious of the common phenomena, fully as far outside man's control as the lightning and thunder and the visitation of blights. Besides, it led so often to that most mysterious of all common conditions, death. Small wonder then that appeal in the case of illness was made first to the gods or the spirits or the devils and ghosts, then commonly believed to control nature by their fickle and changing will. This appears to be a rational explanation of the fact that primitive healing was apparently always part and parcel of religion. The laying on of hands by the Egyptian priests as described in the Papyrus Ebers is perhaps the earliest recorded psychotherapy. The temple sleep of the ancient Greeks is a vastly more modern example. The feather-crowned witch doctors of the primitive savages of the African jungle and the medicine men of our North American

Indians, with their dances, amulets, charms and exorcisms, are no doubt the present living exemplars of the prehistoric primitive psychotherapy that preceded in all races the more developed and modern forms as found in the records of Ancient Egypt.

Little by little knowledge crept in, man's intelligence expanded and he depended less upon prayer and luck and more on knowledge to control the happenings and changes of his environment. This also applied to healing the sick, and thus the barber-surgeon replaced the priestly healer in matters of bodily disease; but he nevertheless plied his art under the blessing, and fortified by the prayers, of religion.

As healing became less an art by virtue of becoming more a science, we see it still further separated from religion, until, in more recent times, through great scientific discoveries, both surgery and medicine became so absorbed in curing and preventing diseases and injuries of the human tissues that the mental side of illness was thoroughly neglected. Neglected, but only temporarily and only by scientific medicine. For into the vacuum which it left rushed the modern healer whose prototype was the savage witch doctor, the Egyptian or the Greek priestly healer. This need temporarily neglected by science was answered, no matter how imperfectly, and so we have with us, even to-day, religious, mystical and pseudoscientific healers, both honest and dishonest.

In the meantime psychotherapy as a hardly or reluctantly recognized branch of scientific medicine was developed slowly, separating the effective elements from the nonsense of former times, until we see Bernheim and others of the Nancy School sift out "suggestion" and recognize it as the active healing element in the magic and mystic cures of their own and ancient times. Thus they found the scientific truth in the effects produced by Mesmer and his followers incidentally giving the needed *coup de grâce* to the still popular belief in "animal magnetism." Suggestion, both with and without hypnosis, was highly developed by the School of Nancy, and suggestibility among major hysterics was given particular study by Charcot and others at the Salpetriere. Suggestion is now recognized as the effective element in every one of the savage, barbaric and ancient civilized forms of supernatural healing, as it is of certain forms of religious healing cultism of to-day. We know now that it is an important element in everyday life, and not only in every sort of unscientific but in all forms of scientific healing, and that it is an essential part of modern scientific psychotherapy.

But until psychology was separated from speculative philosophy and began to be formulated as a science, suggestion alone constituted psychotherapy. Only comparatively lately have psychologists contributed hypotheses that are of practical medical value, so that Medical Science cannot be blamed for not accepting and using what did not exist. During the last twenty years, however, psychology developed hypotheses of human behavior, formulated the phenomena of emotional states and gave to medicine the fundamental basis upon which scientific psychotherapy could grow and has grown.

Within this space of two decades, many hypotheses explaining abnormal states of mind have emanated from the medical world, most of them quite independent of the slowly growing science of psychology and largely ignoring its contributions. Although some of them have added here and there a little light, such as Charcot's and Janet's conceptions of hysteria, and more lately Freud's introspective psychology, yet as we progress we have to discard much that once seemed plausible and take with us only that which successfully withstands the acid test of scientific proof—namely, experiment, experience and agreement with other proved and tried knowledge.

Thus modern psychotherapy has been slowly and painfully evolved, taking suggestion, inspiration, encouragement along with it, but finally depending more and more upon the process of so-called reëducation. By this term is meant giving the patient knowledge of himself and of his disorder, sufficient to enable him to readjust the latter, make the best of such handicaps as he may have, and finally so to arm him with knowledge that he may not again suffer such disorder. Reëducation should be preceded by definitive diagnosis, that is by an understanding, definite and scientific, of the patient's individuality and of his environmental problems. This is what may be called analysis—"psycho-analysis"—had not this term unfortunately become restricted to the Freudian school.

Slowly, but surely, psychotherapy as a part of medical science is making its way to the front, but still the body even of medical scientists do not yet fully appreciate the universality of its application. For still is healing, through mental means, too often considered applicable only to mental disease. In reality, the overwhelming majority of all medical cases are very definitely complicated by a so-called neurosis or a neurotic element, and their need for psychotherapy is so marked that there should be little necessity for further argument in favor of its being accepted as an absolutely indispensable part of every physician's armamentarium. If additional evidence be necessary, consider the physiological concomitants of human emotion. For example, the functional disturbances of internal secretion, circulation, respiration, digestion and muscle tone inherent in, and part of, the emotion fear. Just this glimpse at one of the facts of psychology forces an even wider and more drastic conclusion—namely, that the physician, be he surgeon or internist, has need of psychological knowledge and at least rudimentary psychotherapy in not just a selected few, but in every one of his cases. For they are all of them sentient, emotional, intelligent human beings, no matter what disease they may have, and, whatever that disease may be, even it will be affected favorably or unfavorably by their mental status. Moreover, whatever the physician's therapy, it will be aided or obstructed by the mental effect that it and he produce upon the patient.

EFFECTIVE AGENTS IN ALL FORMS OF PSYCHOTHERAPY

There are certain agents operating in every form of psychotherapy which, by observation and experiment, appear to be the active principles, the elements, though often disguised by verbiage and elaboration, which are ultimately responsible for the effects, be they cures or alleviations, wrought upon the patients.

Suggestion.—In the first place, there is suggestion. We mean by this term the process of gaining the patient's acceptance of an idea without bringing it into contact with his critical faculties. This uncritical acceptance of ideas on the part of a patient depends directly upon the degree of inherent suggestibility which he may possess, and this in its turn seems to vary inversely with his knowledge of the subject to which any given idea is related. Suggestibility also varies in different individuals, from the marked suggestibility of the hysteriacs to almost its disappearing point in the imbecile. It varies at different ages in the same individual, being more marked in children than in adults. In most individuals it may be increased or decreased by changes in their immediate emotional or physical condition. It is present to some degree in all normal people.

Direct Suggestion with Hypnosis.—One method of increasing suggestibility, which presupposes its existence and depends for its success upon the degree of its presence, is hypnosis. Here a sleeplike, trancelike condition is produced in which the patient accepts directly and uncritically the ideas presented. Suggestions of ameliorations or disappearance of symptoms approach, often reach, realization. This state, in unorthodox "cures," is only rarely induced to its full extent, although the Temple Sleep of the Greeks was undoubtedly just this and nothing else. Hypnosis as a preparation for direct suggestion is, however, frequently used in modern psychotherapy and will be more fully described under its proper heading.

Direct Suggestion without Hypnosis.—Without first lulling the critical faculties to sleep, direct suggestion is of little use. To make an assertion that improvement will occur sometime in the future has some value as direct suggestion, for it may not be contrary to the patient's knowledge or belief. But such assertion will have greater effect as an indirect suggestion by manifesting to the patient the physician's belief that such will be the outcome, and, provided he has confidence in the latter's experience and judgment, the patient will *feel* confidence in his prediction. If, on the contrary, the assertion be made that the patient is better, that amelioration has already appeared—*when it has not,* this direct suggestion combats the patient's knowledge and belief and stands little chance of acceptance. Finally, if the assertion be made, no matter how vigorously, that he is now cured, when he is not, the suggestion is in such grotesque contradiction to fact that it is at once discarded as absurd.

However, it is interesting to note that often a suggestion which, when offered by another, is discarded as absurd, may, nevertheless, be more acceptable and often distinctly effective if the patient himself makes the statement to himself. This is the grain of truth at the bottom of the numerous systems of autosuggestion. But, as in direct suggestion from others, here, too, the effect depends first on the degree of suggestibility possessed, and, secondly, on the probability of the truth of the suggestion as compared to the knowledge or belief of the patient.

Direct suggestion without hypnosis is then of very limited effectiveness in all forms of psychotherapy.

Indirect Suggestion.—This is the most useful and most used form of suggestion, and is, of course, used without hypnosis. The suggestion is effective in eluding the critical faculty and fixed beliefs against cure, by its very indirection, its tact. Direct suggestion under hypnosis is comparable to the quickly produced, but short-lived, passive immunity of an antitoxin, whereas indirect suggestion is analogous to the more lasting, active immunity produced by vaccination.

This form of suggestion is used consciously and advertently or unconsciously and inadvertently by every type of healer, orthodox or otherwise, in all cases of all kinds of disease and disorder. Interpretation and conclusion on the part of the patient are the sensitive processes through which the helpful and encouraging ideas and beliefs reach his acceptance. The physician's words are the indirect conveyors of the thought, as the amulet or sacred knuckle bones are also only the agents of conviction of cure. The healer's belief in the power of his prayers or his medicaments is the source of the patient's belief; his words, his incantations, or his draughts are the indirect agents only.

No physician can prescribe a dose of medicine, outline a régime or order a course of treatment—let alone administer the medicine, give the treatment himself, or make an examination or a diagnosis—without using or abusing this powerful, ever-active agent. It is an active working agent in all types of psychotherapy, formulated or unformulated, and is applied consciously or unconsciously by all who deal with illness and disorder among human beings.

Encouragement and Sympathy.—The direct encouragement of a suffering person is an obviously important agent in any form of psychotherapy. No one is free from fear and no one can be in danger or believe himself to be in danger without suffering somewhat from this emotion. Furthermore, fear is a physiological as well as a mental state, which may be distinctly detrimental, especially if long continued. By tactful encouragement fear may be abated, modified, or, if the facts happily do not justify it, it may be eliminated. Anxiety may at least be modified by acceptance. Determination to make the best of it, whatever "it" may be, is a better status than worry, and gives a better prognosis. Important as this obviously is in all cases, it is often neglected by the "busy physician," only to be appreciated and used to the full by the quack.

Sympathy is essential to the tactful use of hope and encouragement. A cold formula, an obviously careless direction "not to worry"—mere words—will not do. Not only scientific knowledge of the patient's disease, but sympathetic understanding of his suffering, is the very basis upon which encouragement grows and hope of recovery or relief is born.

Where one is dealing with the psychoneurotic, these become paramount elements, for, without sympathetic understanding, antagonism will block the most scientific methods of reëducation. Especially is this so of the efforts to utilize the patient's emotions to activate his ideals of conduct and service. To make his suffering the objective of an adventure in friendship, while his symptoms and his disease or disorder are the objective of scientific attack, is a psychotherapeutic ideal applicable to all cases.

Education.—Education is the modern and most useful form of psychotherapy, which in its application utilizes as adjuvants the other elements just mentioned.

It uses primarily the patient's intelligence. Its object is to give him knowledge of his own difficulty, of his own assets and liabilities, and finally to teach him how to adjust himself to these difficulties. In the psychoneurotic, education aims at realization by the patient of his own fundamental normality, in spite of functional disorder; whereas, in the organically crippled, it aims at revaluation of symptoms on the basis of their actual significance and at development of such abilities as would minimize the handicap. Its method is that of teaching the patient to think, both of himself and his difficulties, objectively, practically and effectively, so that he may be successful in his adaptations to his world as it actually exists.

Obviously this method is particularly useful in dealing with the psychoneuroses. It is also, however, applicable to the psychoses which so often exhibit a very large and active psychoneurotic element. Also, in varying degree, with variations in technic, it is applicable to a majority of medical and surgical cases, such diseases being often complicated by psychoneurotic disorders.

With the individual as with the community it does little good to order or legislate health measures, unless such orders or legislation have been preceded by education. It is only thus that we can expect intelligent coöperation. To this end, then, in all cases, reëducation should be employed (the technic and detail being fitted to the intelligence and educational status of the individual). Thus the object of each element of the proposed treatment, each step, each order, should be given its real significance. The object of the medication, the procedure, or whatever it may be, should be made clear and intelligible, and its possible, probable or certain effect foreshadowed. This principle of psychotherapy, intelligently applied, is of great assistance in all cases, whether medical, surgical or mental, for it results not only in mutual understanding but in intelligent coöperation between patient and physician.

Increasing the effectiveness of intelligence through education is thus the most difficult, but so far the most successful, type of psychotherapy. It may also be said to make the most effective use of the other agents described: namely, suggestion, encouragement and sympathy. Educational psychotherapy is furthermore of universal application as Mental Hygiene. In this aspect it is capable of much, and is growing steadily. Its application, especially in childhood, is of the greatest importance, for here the old adage that "an ounce of prevention is worth a pound of cure" holds true with peculiar force.

Forms of treatment which aid psychotherapy, either because of their suggestive force or because they directly affect the disturbed physiology, are worthy of notice. Prolonged rest with isolation and with or without overfeeding is of value only in cases where the physical condition is akin to bankruptcy, when there are definite and unavoidable indications in a metabolic and physiological unbalance which in themselves demand correction. Otherwise, particularly in the psychoneurotic conditions, rest cure at best relieves symptoms only temporarily and leaves the patient even more sensitive, more maladapted than ever.

Electrotherapy, unless it be applied to exercise paralyzed muscles, is of value almost exclusively because of its suggestive force, and its use should therefore be limited to those cases for which suggestion is suitable and advisable.

Hydrotherapy, as such—exclusive of ordinary bathing for cleanliness, the use of stimulating baths for "tonic" purposes and continuous warm baths for their direct sedative effect—is of purely suggestive value.

Dietetics is of use in all cases, but certainly is no more so in cases requiring psychotherapy than are any other of the physical aids to good health, and like all the others it may be made of suggestive value.

The use of glandular therapy and its relation to disturbed metabolism and to disorders of the nervous system is still a matter of doubt and speculation.

We have space only for the mention of serums and vaccines and other forms of physical therapy, the relationship of which to psychotherapy is perhaps too obvious to call for demonstration in so short an article.

It should be noted, however, that all forms of therapy just mentioned are not only capable of aiding our psychotherapeutic efforts and, in turn, of being aided by such efforts, but that there is great danger, especially when dealing with mental and nervous disorders, of *over*emphasizing their importance: grave danger on the one hand of leading the patient to expect too much from such agencies, and on the other, especially in the psychoneurotic, of producing a too great dependence on such physical measures. Thus inadvertently may be produced disappointment and discouragement, or a greatly increased hypochondriacal sensitiveness to physiological conditions.

This danger, however, does not apply to Occupational Therapy, which is of great value in convalescence of all types of cases and in the active treatment of many. Through it the patient may learn to overcome his handicaps, through it he is saved the introspective miseries and dangers of idleness, and through it directly and indirectly he rebuilds or strengthens his sense of identity and his self-confidence.

INFORMAL PSYCHOTHERAPY

General unformulated psychotherapy is not only applicable, but is indicated in varying degrees of urgency, in all forms of illness, disease or disorder. The degree of urgency depends of course upon the nature of the case—that is, whether it be primarily mental, or how great the mental element may be. This element, however, is never altogether negligible, no matter what the disease, and therefore one can say positively that psychotherapy is never under any circumstances to be neglected. For the principles, the effective elements upon which it is based are always working for or against the patient, whether the physician wills it or not or whether he is aware of it or not.

Hope.—Among these elements which may be used by the physician to the patient's advantage, or neglected by him to their mutual disadvantage, is the suggestive value of optimism. A cheerful manner, a hopeful attitude are obviously contagious and therefore helpful and inspiriting. Perhaps due to its obviousness, as well as because the physician is sometimes too much occupied by a sense of the seriousness and dignity of his calling, this particularly helpful factor is neglected.

Faith.—Another important element in unformulated psychotherapy is the confidence of the patient in his physician. This confidence can hardly be produced to-day by the archaic method of inducing an awe-inspired belief in the physician's supernatural power, his magical skill or his superhuman infallibility. It should be established, however, and can be, on the grounds of the physician's earnest and unflagging determination to do everything in his power for his patient's welfare. By showing that this determination is not only earnest but sympathetic, not only sympathetic but intelligent, unprejudiced and single-minded in purpose, the physician has no need of the false cloak of the magician nor the claptraps of the charlatan. He need only be an honest man. The suggestive help he gives is indirect and powerful, and the patient both feels and knows that he is "in good hands."

Coöperation.—This powerful ally, the patient's confidence in his physician, can also be greatly increased by the physician's confidence in his patient. To *expect* coöperation from one's patient is the first step toward getting it. This attitude is not only a positive help, but also goes far toward avoiding the pitfalls of antagonism, especially in intelligent, high-spirited patients who naturally resent being treated like morons or naughty children. Furthermore, by indirect suggestion, it greatly enhances the patient's respect for the intelligence of his physician, and therefore his confidence in him as such.

Courage.—An element not to be neglected is encouragement. This can be done directly by deliberately picking out the most hopeful probabilities, the most encouraging signs and proofs of improvement, as well as by pointing out the ultimate cure to be hoped and tried for. If the facts are such that this cannot truthfully be done, then at least such amelioration as may be hoped for should be emphasized. And above and beyond this, one can at least emphasize the importance and benefit of every favorable factor of the present day or hour. Lastly, one can always encourage one's patient to make the best of the present and to value quality rather than quantity of life.

Sympathy.—The relation of physician to patient should be marked by that sympathetic understanding and respect upon which any adventure in friendship depends for its success, upon which, in other words, any successful contribution to another's welfare must be founded. Not only to understand, but to show that you heartily *wish* to understand, is an important aid in establishing mutual confidence and coöperation.

Suggestion.—Indirect suggestion has already been mentioned as an important element in all forms of psychotherapy. It is the potent factor in much of the informal "mental effect" we produce upon one another, and may be helpful or harmful, according to the degree of intelligence with which it is used or the degree of unintelligence with which it is abused. A drug may be administered, and have its physiological effect enhanced considerably if it be exhibited suggestively (namely, patent medicine successes). A homeopathic physician, whose drugs certainly possessed no physiological potency, was justly famed for his "cures." He always administered his own drugs, but was especially fond of powders, and it was said that his manner of placing a powder on his patient's tongue and then saying "There!" was the whole secret of his success. A good example of the power of indirect suggestion.

Direct suggestion under hypnosis obviously has no place in general unformulated psychotherapy as applied to general practice, for it requires an especial technic and is of very limited use, and that chiefly among hysteriacs.

Direct suggestion without hypnosis is of considerable use, however, in surgery, though it is rarely used. It has been found most useful in quieting and securing the coöperation of alcoholics during the initial stages of ether anesthesia. By direct suggestion the terrific primary excitement induced by ether in these cases can be greatly modified and sometimes altogether avoided. The scope of this chapter, however, admits only of mentioning this use of suggestion.

Adverse Suggestion.—Adverse suggestion is the reverse of the medal. All patients are more or less suggestible, no matter what their particular disorder may be. Therefore, suggestion is not a passive tool, to be used or laid aside as the physician may choose. Whether he will or no, his patient continually receives from him, from everything he does or says, harmful or helpful suggestions. The help that may come from the deliberate and intelligent use of indirect suggestion is offset by the harm that may be done by the unintelligent, inadvertent neglect of this powerful influence. Adverse suggestion is the very reverse of therapeutic suggestion and it will work its harm, unless it is deliberately guarded against.

The dangers of adverse suggestion in all cases begin with history taking. Questions as to the neuropathology (insanity, suicide, alcoholism) of antecedents, as to the incidence of tuberculosis, cancer, heart disease in the family, are often necessary, but are redolent of adverse suggestion. They may be harmless or even helpful, not only according to the facts revealed, but principally according to *how* the questions are asked and what significance they are deliberately, inadvertently or carelessly given by the inquirer. The questions may, for instance, be prefaced by the statement that certain statistics of very questionable value, with little bearing on this particular case, are being sought largely as a matter of historical routine. Each favorable fact may be commented on as it is revealed, and each apparently unfavorable fact discounted on the most favorable terms. Or, on the other hand, the inquirer may plow into the matter with keen, sleuthlike intent and pause with a dubious shake of the head at each answer. The favorable or unfavorable impression on the patient is a result of far greater importance even than the information elicited—which is much the same, whichever method is employed. Obviously only *necessary* information should be sought. Also obviously, whenever possible the family history should be obtained from some one else beside the patient.

Another danger due to suggestibility is often overlooked in taking a history, and that is the suggestive effect of a leading question. The suggestibility of the patient, influenced by the implication of a leading question, is apt to distort facts if not actually to falsify them. Leading questions should therefore be avoided not only because of their possible adverse effect on the patient, but also for the sake of accuracy.

Physical examination is another opportunity to use or abuse suggestibility. It should be remembered that the patient is undergoing, to him, an unusual and disquieting experience, though it is a usual and very ordinary procedure for the examiner. Too often the physician takes this opportunity to impress his patients with his own dignity and the seriousness of the occasion (a reversion to witch doctor methods), and succeeds only in mystifying and frightening his victims by his ponderous solemnity. Physical examination is, on the contrary, an excellent opportunity to show skill and quiet efficiency by the elimination of all unnecessary details, and to impress the patient with the keen and *hopeful* interest of the examiner. It is likewise an opportunity for favorable comment on the conditions found, whenever such comment is justified. To have one's organs passed in review, searchingly and critically, is to any one an unpleasantly anxious occasion, and it should be made as brief and as little suggestive of suspicion as possible. A thorough examination should of course always be made, especially in young children; but in the case of adults, whose suggestibility through experience and misconception has been educated, no unnecessary extra examinations should be made. A method which puts all patients through every possible physical, laboratory and X-ray examination as a matter of routine, even *before* the personal conference with the consultant, cannot be too strongly condemned.

Personal Attitude.—One of the adverse influences of suggestibility, especially marked in the ward treatment of medical and surgical cases, but even more marked in nervous and mental cases, is the decrease or even total loss of the patient's sense of identity. This is particularly true of late years, where less medicine is prescribed, therapy is much simplified, and there is less manifest personal interest in the lesser discomforts and minor daily changes in each individual patient's functional fluctuations. The greatly increased, purely scientific interest in his pathology, it is to be feared, has overshadowed the manifestation of personal, individualistic interest of the physician toward his patients. This loss of identity is an obstacle to therapy and is quite unnecessary, for an interest in prognosis, that most important of all aspects of scientific medicine, and the most difficult, leads directly to consideration of each patient's life as a whole, his abilities, opportunities, purposes, plans, and why not also his ideals and hopes?

The impersonal attitude can be overdone. It is appropriate, and in every way useful in considering a pathological lesion and in evaluating the symptomatology of a disease; but when it includes the patient himself, it is adverse in its suggestion, and definitely bars the patient from a benefit which he deserves and needs. To understand the disease is essential; that is obvious. To understand the patient is also essential and this he rightly demands. To have a sympathetic understanding of an individual's needs, of his handicaps, of his assets in life as well as his liabilities, in no way disturbs or runs counter to the scientific ideal of impersonal understanding. Rather it rounds the latter out and points the way for its practical application as therapy, especially as psychotherapy.

The manner as well as the words of the physician is of significant importance. We express our interest or lack of it, our understanding or misunderstanding, our point of view, our determination or hesitation, as well as our hopes, fears, likes and dislikes in manner quite as much as by words; and manifestly manner is a method of indirect suggestion, powerful, therefore, for good or evil.

A gross example of crude adverse suggestion is given by the hesitant physician who "thinks aloud." He seems to talk to himself while he examines. As a matter of fact, he is talking to the patient, protecting himself against future responsibility for error. "You may have rheumatism, but I don't *think* so. There may be an intestinal upset or possibly a touch of grip." What he really means is, "I *think* I know what's the matter but I'm not sure, so I divide the responsibility with you. I'm afraid to be wrong and won't take that risk, and so I'm hedging."

Medical self-protection is harmful to the patient, and there is no reason for it except the timidity of the physician. He must be willing to be found mistaken. He must be satisfied to do his best and take the consequences. Honesty, intellectual integrity and earnest effort are the best guarantees he can give his patients, and with these he needs no safety-first devices for himself. To share his doubts and worries with his patients is both selfish and harmful. He can avoid positive statements where the facts or absence of facts make this necessary, and he can always find a consultant with whom to share the responsibilities when these are really heavy and there is reasonable doubt.

Psychotic and Psychoneurotic.—All that has been said of the dangers of adverse suggestion in regard to general medical and surgical patients applies with redoubled force when one is dealing with psychoneurotic patients who are always hypersensitive. This is also true of psychotics, who are often largely psychoneurotic, and therefore quite as sensitive.

The first contact with these patients is of the greatest importance. Amusement over their vagaries, contempt for their points of view, anxiety and doubt, may easily show through the veneer of the physician's manner, and, feeling these things, the patient withdraws still further within himself or has his latent antagonisms thoroughly aroused. The result is the opposite of contact—it is insulation. Such an occurrence is particularly unfortunate in view of the importance in these cases of the complete co-operation of patient with physician, which is so necessary to securing a complete history.

Respect.—Disrespect and unbelief in the reality of his suffering is always suspected by the hypersensitive patient, and he therefore feels it only too quickly and surely if it is there. When this happens, the physician is often cut off from further usefulness in the case. Prejudice of this sort, like most prejudices, is based on ignorance and for this reason, as well as because it arouses natural antagonism, is an absolute bar to successful psychotherapy.

FORMAL PSYCHOTHERAPY

SUGGESTION

Suggestion, as already stated, is a useful method in informal, general psychotherapeutic efforts. It is also an accepted and important method of formal, definitive psychotherapy.

It depends on a characteristic, common to all normal human beings, to accept ideas uncritically. It varies in degree in different individuals, inversely to their knowledge rather than their native intelligence. It is greater in children than in adults, practically absent in idiots and the aged, often absent in organic psychoses. It varies at different times in the same individual, depending upon his emotional and physiological status. Fatigue apparently increases suggestibility, as does pleasant emotional tone; whereas depression, restlessness, excitement, pain or bodily discomfort diminish it. Confidence in the authority and honesty of the source of suggestion is, of course, essential to its ready acceptance. Therefore the manner, words, and expression of the physician have great effect in increasing or decreasing the power of his suggestion.

Indirect suggestion—that is, suggestion through inference—is the method to be preferred, as it is in complete harmony with, and may greatly enhance the effect of, the other therapeutic measures. It is useful in all cases, as suggestibility is present to some degree in almost every one, but it is particularly useful in formal, reëducational psychotherapy as applied to psychoneurotics. By this method the value of a patient's symptoms, relative to his organic soundness, may be reduced to a normal level, at the same time that his education is progressing. Tactfully applying emphasis on the strong points of his physique or letting him infer one's complete belief in his success, either as a working citizen or in his particular job—this is to suggest indirectly that his malady is being overcome or, at worst, is only a temporary handicap. To supply him with influential evidence of his own normality, of the value of his intelligence and character, is not only of inspirational value, but also indirectly suggests the relative unimportance and temporary character of his symptoms.

Indirect suggestion is of value, but to a less degree, in psychotic conditions. Where there is deterioration, it is, of course, of least use.

Direct suggestion, as stated above, is of little value in any case without hypnosis, and with hypnosis it is of value only to remove obstructive symptoms in hysteria major. It is also used in hysteria to uncover unacknowledged or forgotten emotional experience which may bear causal relation to the disorder, and the discovery of which might aid in re-establishing normality.

There is grave danger, however, in using hypnosis in cases of severe emotional disturbances, especially in psychotic states. The danger lies in the liability of increasing the severity of the emotional disturbance, in increasing delirium, feeding delusion and actually activating a latent hallucinosis.

In hysteria, however, hypnotic suggestion is of definite though limited use in removing functional disturbances, such as amnesias and paralyses. Here again there is danger that both patient and physician may be so satisfied at having removed the symptoms, that they neglect the underlying condition, and the patient still has hysteria, though without the lately removed symptoms. This involves the liability, not only of his developing other symptoms in the near future, but, because of such symptoms, of his seeking further aid from suggestion. A series of treatments of this sort almost inevitably produces a dangerous dependence of patient on physician, as well as an increase in the patient's liability to develop still further his tendency to dissociation.

Carefully applied, and used only in close conjunction with the reeducational method, suggestion under hypnosis for the purpose of removing obstructing symptoms is a useful and proper form of psychotherapy.

Technic of Hypnotic Suggestion.—Hypnosis is a process of heightening suggestibility. It can be done only with the patient's acquiescence and coöperation, for it depends largely upon his willingness to accept suggestions of wandering attention, of uncritical dreaminess, of approaching sleep. As a matter of fact, the patient merely follows the directions of the operator, and thus by autosuggestion induces in himself hypnosis or a hypnoid state.

The conditions favoring hypnosis are:

1. Narrowing the field of consciousness by fixation of the attention upon monotonous sense stimuli.
2. Restriction, by muscular relaxation, of voluntary movement.
3. Inhibition of ideas not directly connected with sleep, by concentrating the attention on that of sleep.

To induce these favoring conditions, the patient reclines in an easy chair or on a couch. He is instructed to relax arms, legs and trunk muscles. He is to pay no attention to what is going on about him, to discard all extraneous ideas and to fix his mind exclusively on the ideas and sensations brought to his attention by the speaker. A crystal or some other bright object, or even a pencil point, may be used as the target for his attention and his gaze. This object is held in front of his eyes at a distance of ten or fifteen inches, slightly above the normal plane of vision. Held thus, the extrinsic muscles of the eyes soon weary of the effort, as do the muscles of accommodation. The patient is instructed at first to focus carefully on the brightest spot on the object, and at the first signs of eye fatigue he is told to look through it as though it were a great way off. Suggestions may then be given, starting on a basis of fact, that his eyes are growing sleepy, his eyelids heavy, and the object is becoming blurred. Suggestions are then given that his body is relaxed, that his hands and feet, and then his legs and arms, also feel warm, comfortable and relaxed. The object is moved slightly nearer and slightly farther above the normal plane of vision as the pupils dilate.. As the eyes become suffused and the extrinsic ocular muscles show further signs of fatigue, more positive suggestions are given that the eyelids are heavier, that they are drooping; finally, that they are closing. As the eyelids close it is well to stroke them gently, suggesting that they are lightly but firmly closed, as in sleep.

Then, resting the fingers lightly on the patient's forehead, further suggestions of sleep are given, such as "Your body is relaxed as in sleep. Your breathing is quiet, regular, slow and deep. You hear my voice clearly. You have let your mind 'go' entirely. It is now under my direction. You need not try to listen, for you will hear and believe even when my voice seems to come from a great distance. I am talking to you in your dreams. You will continue in this state throughout the treatment. This relaxation of mind and body is healthful and helpful. All interference is removed and your fundamental normality restores itself. You are getting not only rest, but refreshment and readjustment in this sleep."

Suggestions, even the general ones, must of course be varied to suit the particular personality, education and disorder of each patient. The above samples are offered only as being appropriate during the induction of hypnosis.

Next, the specific therapeutic suggestions should be "poured in." Simplicity, directness and incisive repetition are now in order. For instance (in case of hysterical paralysis): "Your leg is limber, the stiffness has left"—"Your leg is loose-jointed, soft, pliable, and I move it easily in every direction"—"Your leg is well"—"It is entirely well." Each suggestion should be repeated distinctly three, four or more times.

The approach to the positive "cured" suggestion may be more gradual. That is, the above suggestions might be preceded by "Life is coming back into your leg"—"It feels warm"—"You now feel it tingling"—"It jerks a little"—"The muscles are waking up," etc., etc.

Suggestions should then be made in regard to the general effects of the treatment. "You will feel refreshed, rested; your head will feel cool and clear, your body invigorated," etc. "You will feel as though you had had a most refreshing nap."

It is well to repeat all the important, specific, curative suggestions again before waking the patient.

Suggestions as to awakening are then given. The memory of what has gone on during treatment may be suggested as vague or absent, according to the depth of hypnosis obtained, and posthypnotic suggestion may also be given. But unless the hypnosis has been deep, they are not at all apt to be successful and, if they fail, they may through that failure have a distinctly unfavorable effect on whatever else has been suggested.

Suggestions for awakening should aim at obtaining a gradual, normal return to consciousness, with feelings of refreshment, as from normal sleep. To this effect one can say, for instance, "You will rest here for a little time, comfortable, relaxed, dozing, until I return. I will then count up to ten, and at ten you will open your eyes. You will awake refreshed, rested and (if hypnosis has been deep enough) cured. You will 'stretch,' perhaps yawn, and will feel that you have had a fine nap." The operator can then leave the room quietly and return as promised in five minutes or half an hour to wake his patient. Or he can be awakened immediately, omitting the rest period, and using the same general formula. The final stage is accomplished by saying, "Now, as I count, you will gradually become more and more alert, until, when I reach ten, you will be completely awake, refreshed, rested," etc. Holding the fingers on the patient's forehead, the operator begins to count slowly, softly at first, but progressively more loudly, letting his fingers rest ever more lightly on the patient's forehead, till, at ten, he lifts them suddenly and completely, pushes his chair back, and ends the treatment.

When hypnosis is used for the purpose of eliciting information in regard to "forgotten memories" of possible causal relation to the patient's disorder, the same technic is applied throughout, save that suggestions as to complete memory are made, and the patient is allowed to relate them "as in a dream." The crucial point of this procedure is at the moment of awakening, when every effort must be made to keep the recovered memory in the patient's mind *during* the awakening, by repeatedly recalling, by interlarding the suggestions of waking with those of the memory. The awaking process should be made as short as possible, without shock, with this end in view.

In General.—It is well in using hypnosis, particularly with hypersuggestible subjects, always to suggest during the treatment that they never will allow any one except a doctor to hypnotize them, nor for any purpose except the specific one of cure. It is also well when hypnotizing women to have a third person present.

If results are not good, attempts at hypnosis should not be repeated after the first few trials. Nor is it wise to continue to use hypnosis on a patient after the obstructive symptoms have been removed or ameliorated, for there is danger, if not certainty, of producing increased suggestibility and increased liability to dissociation by often repeated hypnotic trances. There is also danger of inducing somnambulism and, through it, catastrophe.

The technic must be varied according to the needs of the individual patient, according to the degree of his suggestibility and, lastly, according to the personality and ability of the physician. Some patients are suggestible only to a very small degree, and it is waste of time to attempt hypnosis on them. Only a mild, restful, hypnoid condition may be induced in them, which is of little use for direct suggestion. Furthermore, they are not the type which exhibit hysteric symptoms, and there is consequently no indication for hypnosis.

In short, hypnosis is of very limited use as a therapeutic method. It should be used only for the removal of symptoms, and then with great caution. It is of still more limited use as a diagnostic aid. When a disability, such as a tremor or a paralysis, is of questionable nature, its disappearance under hypnosis classes it unquestionably as hysterical. However, this method at best could only be used to obtain confirmatory evidence, and one obviously could not depend upon hypnosis as a reliable or ultimate diagnostic means.

As a combined diagnostic and therapeutic agent, hypnosis is of some value in discovering and reassociating emotional reminiscences. But it can hardly be considered as reliable and dependable as the direct, careful questioning and common sense analysis which uses the coöperation of the patient in his normal mental status. Nor is it comparable to the latter method in success. Indeed, it has proved itself only of slight use for this purpose, even in the hands of the most expert, and cannot be recommended to the less experienced.

Hypnosis is not a system of therapeutics in itself. It has its dangers and disadvantages, which, in all cases but those of hysteria major, outweigh its possible benefits. Therefore it should be used only in such cases, and with due care to avoid its aforementioned untoward effects, not the least of which is the induction of abnormal dependence of patient on physician. Thus its chief if not only use is the temporary removal of an hysterical symptom-complex, *without* affecting the underlying cause.

Reëducational (Rational) Therapy

Psychotherapy, especially reëducational psychotherapy, is indicated in all psychoneurotic disorders, but, as a great majority of psychotics suffer from an overlying psychoneurotic element which materially affects their progress, this form of therapy may also be used with benefit for these cases. Thus, although what follows applies chiefly to the treatment of the psychoneuroses, it may—and should—also be applied to the treatment of the psychoses, with such modification of technic as the limitation of intelligence and activity of the emotional states may dictate.

Basis of Reëducational Method.—The basis of reëducation is normal psychology on the one hand and abnormal psychology on the other. In short, an understanding of the problem of human adaptation, of the failures of adaptation—especially those failures called "psychoneurotic"—is essential to psychotherapy. Not only this general knowledge is necessary, but there is also the specific necessity in each case of understanding the individual as a special problem, in which this general knowledge is applied individualistically. This, in the broad sense of the term, is psychoanalysis, and is *not* necessarily Freudian. If one accepts the premises of Freudian philosophy and finds in it a satisfactory explanation of human behavior, then a thorough study of its psychology and the writings of its followers would be indicated, in order that its methods and technic might be applied. However, although what follows includes some of the mental mechanism postulated by Freud and Jung, it is based only on the accepted facts of psychology and sets forth a method of analysis and a technic of reëducation which, though far removed from perfection, has definitely proved its worth in practice.

Psychology of Adaptation.—In order to understand the problem of maladaptation, it is necessary first to survey briefly the usual processes of man's normal adaptation.

The factors of this equation of human adaptation are: first, the material to be adapted, that is, the individuality; second, the conditions to which it must be adjusted, namely, the environment; and third, the process of adjusting one to the other—in short, adaptation itself.

Taking these factors in the order named, we have *individuality* as our first puzzle, and in order to bring it to terms, we must define exactly what we mean by individuality. For the sake of clearness, we limit the meaning of this term far short of the vague universality which it—in common with such terms as personality, temperament, character, intuition, instinct and indeed any other term relating to the mind or spirit of man—has acquired in common parlance and in popular, religious, "psychic" and romantic literature. As the mathematician deliberately and coolly says, "Let 'A' equal such and such," so we shall say, "Let individuality equal the sum total of the native and acquired predispositions of the individual, and let it also include *temperament* and *character*" (the latter terms to be defined presently). Let us call the sum total of instincts and other inherent predispositions *personality*. The individuality is, then, to be considered as a composite made up in the first place of instincts and other inherent predispositions—these being the raw material, personality—and, in addition, of temperament and character, which are distinctly qualitative factors modifying the raw material.

What is this primary raw material, instinct? A clear and practical definition of instinct is that given by McDougall in his book on *Social Psychology*.[1] He defines instinct as "an inherited or innate psychophysical disposition which determines its possessor to perceive, and to pay attention to, objects of a certain class, to experience an emotional excitement of a particular quality upon perceiving such an object, and to act in regard to it in a particular manner, or, at least, to experience an impulse to such action."

Let instinct, then, mean a hereditary, inherent disposition or tendency to respond in a specific manner to a specific change in environment. We may say further that instincts are the chief, outstanding, inherent dispositions to action, and that they, together with other less specific inherent tendencies, both inherited and acquired, constitute the gross adaptive mechanism, the raw material we have called personality.

But let us inquire more closely into the intimate mechanism of this dynamic factor, instinct, before considering the other elements making up the total individuality.

A reflex is the simplest form of adaptive mechanism. It consists, roughly speaking, of three parts—afferent, central and efferent—involving the familiar sensory-motor arc, but rising to no higher level in consciousness than the sensations involved in the reaction. Now a reflex may be considered the simple prototype of the instinct. It has to do, however, with adaptation of only a limited part of the body to a change in environment, whereas an instinct involves the response of the whole.

Like a reflex, an instinct has, roughly, three parts—sensory, perceptive and motor. The first or afferent part involves the sensory nervous mechanism; the central has to do with perception and the affective part of emotion, and involves the forebrain; while the third or efferent part involves the motor nerves, including the sympathetic, and has to do with the visceral and somatic part of emotion, as it mobilizes the body for the appropriate specific action—instinctive adaptation.

Each instinct has its own particular emotion which is the very keystone of its dynamic arc. For instance, the instinct of escape has fear as its peculiar emotion, the instinct of pugnacity has anger, and so on.

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[1] Social Psychology (10th ed.), page 29.

An instinct may then be said to be a much magnified and compounded reflex, involving the response to environment, not of a single part of the body, but of the whole animal. The primary emotion which belongs exclusively to its own particular instinct, and can be aroused only as part of that instinct, is that element which we "feel" both as a "feeling" and as an impulse to specific action, and which, largely through the sympathetic nervous system, but also through the central nervous system, rearranges the glandular activities, puts the musculature in readiness, and appropriately energizes the cardiorespiratory and other "systems," thus mobilizing the body for immediate and specific action.

How many and what are the primary instincts composing personality? That is a question which should not be too definitely answered in the present state of our knowledge. But for the practical purposes of the physician, the instinctive predispositions may be roughly divided into those which apply particularly to self, and those, on the other hand, which have to do with race or herd. Thus, under the first head, we have self-preservation with its two oppositely acting factors: (1) escape, motivated by its proper emotion, *fear;* and (2) pugnacity, with its emotion, *anger.* Then, among instinctive dispositions which are distinctly for the herd, we have the gregarious impulse and the constructive and acquisitive instincts; while the mating and parental instincts obviously have to do with the preservation of the race or species.

Among the less specific instinctlike tendencies, McDougall adds to this list Sympathy, Suggestibility, Contrasuggestibility, Imitation, Play and the Emulative Impulse.

Gross behavior of the individual animal may be said to be determined primarily by the action and interaction of the instincts just enumerated, in response to changes in his environment.

In the other animals instincts are aroused only by their appropriate objects. In the superintelligent animal, man, however, an instinct may be aroused by the *idea* of that object, by a similar object, or indeed by a dissimilar one which is only indirectly associated with the primary object. It takes a loud noise to set in motion the instinct of flight of a bird; whereas the memory of an explosion or the thought of an impending danger is capable of arousing this instinct in man. Furthermore, man is conscious of self—which the other animals, presumably, are not. He pictures himself in any situation which concerns or may concern him, and may thus go through, in an imaginary way, scenes more or less dramatic; and, going through them even in his imagination, the appropriate instincts will be aroused. He will be conscious of them in terms of their emotion, and also in terms of their specific impulses to action.

Where several instincts are simultaneously aroused by a complex change of environment, the resultant response must manifestly be the action, either of an instinct overwhelmingly stronger than the rest, or of a conflict between instincts more evenly matched. Animal behavior is thus practically determined by the sum total of its instincts—its personality. Certain changes may, however, be acquired by training, so that a specific stimulus no longer motivates its appropriate instinct. Experience in the simplest form—training, as in domestic animals—may thus modify instinctive action. But, on the whole, the personality of the animal remains about the same—timid, pugnacious or gregarious as the case may be—and he continues to behave accordingly.

By means of instinct, personality then adapts itself to environment rather reflexly—rather wonderfully, to be sure—but still rather stupidly. Personality cannot think ahead or backward, or indeed at all, and so is dependent for action on immediate circumstance.

In short, man's instincts become educated to respond to a greatly increased number and variety of stimuli. For instance, the "self instinct" becomes sensitized to respond to any threat, actual or implied, not only to his physical well-being, but to his ethical, social or mental integrity, to anything, in fact, which he can label "my"—my life, my child, my reputation, etc.

Superimposed upon all this instinctive apparatus and self-consciousness, man has in addition the power of choice, which animals evidently have not. His instincts, just as in all the other animals, are in more or less continual conflict. First one and then another gains supremacy over the rest and expresses itself in action. But, unlike animals, man may choose which of the conflicting instincts is to carry itself out in action. The game rooster presumably has no choice on seeing another of his kind, for his instinct of pugnacity is aroused and his anger must express itself in fighting. Man, on the other hand, even though angry, may fight or run, or even return good for evil, as he chooses.

But with all his intelligence, consciousness of self, and power of choice, man can affect directly but one part of instinct, namely, that of expression. To be sure, the ingoing or receptive portion of an instinct may be changed by training and education, so that it no longer responds to a specific object. For instance, a bird may be taught, by combining the giving of food with the ringing of a gong, to respond to it as a signal for food rather than as a signal for flight. And so, by experience and education, man may be taught not to be afraid of things from which the primitive instincts would have driven him to fly.

The central part of the instinct, that is, the emotion which tends to express itself in specific action, is immutable; it cannot be changed. If an instinct be aroused, its central or emotional part must and will follow inevitably. From this we draw the important conclusion that one cannot be held responsible for the presence of emotion. One cannot help being angry, one cannot help being afraid, and this holds true for any other primary emotion.

The one part which *is* under the dominion of choice, under the direct power of the will, is the third part of the instinct—its expression in action. Man's responsibility for self-guidance begins and ends with this part.

Realizing that man may choose to which one of his conflicting instinctive impulses he will give expression—knowing that he can, by an act of will, change the weaker of two conflicting impulses into the stronger—we may ask what influences his choice, independent of, even contrary to, the strongest instinctive forces. We must confess that here there is a gulf in our knowledge. We cannot evolve the superior force from the lower physiological mechanism, nor can we find its origin in the highest and most subtle mental mechanism. It may be a so-called "higher" instinct, a product of biological evolution; or, to avoid religious disputation, call it "spiritual force." We do not know where or how it comes in. Its origin is supersensible, but it is there. This force manifests itself in the inner and higher self which presides over the lower, self-conscious, sensory-motor apparatus, and through its executive, the will, it finally determines the behavior of what would otherwise be the mere animal man.

The behavior of the higher animals is, then, determined by the conflict of instincts, the stronger in each instance winning out and expressing itself directly in action, whereas man's behavior is determined by the action of his will upon this conflict. He uses the energies liberated by the instinctive mechanism, but by means of his will he guides the expression of these energies so that they may correspond to certain higher standards—social, moral and spiritual. Man is, therefore, not merely subject to conflicts of instinct, but to conflicts between whichever may be the dominant instinct and the ideal which stands in opposition thereto. Any resultant action must then involve the temporary defeat of either the instinctive impulse or the ideal, or it must result in a compromise or a stalemate.

Temperament is another element upon which man must use his power of choice, his guiding will. By temperament I mean an inherent tendency, as inherent as instinct, but involving the affective side of emotional life, and very likely determined somewhat by the physiological status, acquired or inherited. It is a qualifying element difficult to define—but in effect it predisposes the individual to over-respond or under-respond, to be oversensitive or insensitive, as the case may be, to the more or less specifically painful or pleasurable elements in his emotional activity. This pain-pleasure element of emotion is to all of us an important motivating influence, but some are more sensitive to it than others. The degree of this sensitiveness is, however, directly amenable to training and power of choice, and therefore, if abnormal, can be considered from the therapeutic point of view as a temporary evil, if it be an evil at all. For instance, such sensitiveness may stay just sensitiveness, or it may be developed into specialized and purposeful appreciation. We may thus have an apathetic, a cheerful or a gloomy temperament as an asset or a liability, as the case may be.

The last element on the personal side of the adaptation problem is *character.* Again we shall have to give this term an arbitrary limitation in the manner of the mathematicians. Let character stand for the sum total of the effect produced by choice and intelligence—applied according to social, moral and ethical standards—upon the reactions to environment of the raw material of personality and temperament. Thus a "strong" character is one which realizes its ideals and purposes in action, whereas a "weak" character may have high ideals, but expresses them in action either imperfectly or not at all.

Individuality is then *personality,* modified in its reaction to environment by *temperament* and *character* (that is, *intelligence*).

As to the factor of environment in this problem of adaptation, it includes all the end products of the personality. For it is composed manifestly of countless other individuals as well as the obvious physical elements, beneficial and harmful to the individual and to the race. This factor may, therefore, be roughly divided into the physical and social. The physical elements in civilized life can hardly be said to constitute a psychological problem in themselves, except for a very different class of case from that with which we are now concerned. The social elements, however, are those elements which are the products of civilization on the one hand, and, on the other, present the very difficulties which test one's adaptability.

The history of civilization's emergence from savagery is repeated in many respects in the evolution of the individual from irresponsible babyhood to citizenship. Child-training, "upbringing" and education constitute the chief environmental aids towards attaining more skillful, more intelligent and more unified adaptation, towards guiding and forming the growing individuality from the unintelligent, instinctive level to the intelligent and ethical. It is thus that habitual attitudes are formed and personal moral traditions established. Environmental influences are baneful or beneficial very largely, if not exclusively, from this point of view.

Of course the social environment may be too easy or too hard. It being too easy, that is, arranged to adapt itself to the individual demands, it "spoils" the individual, and a grown, spoiled child results. It may be too hard, especially prematurely too hard, demanding an adaptability that the individual has not attained, thus forcing him to regard the adaptation as impossible, the world as his enemy, and throwing him back into an unsocial, self-protective (instinctive) attitude.

However, environment rarely, if ever, furnishes in itself the causative factor in the therapeutic problem of the psychoneuroses, except from the point of view of early influence, training, education and suggestion.

Therefore this aspect of the problem has to do only with prevention, not with cure, and belongs to the realm of Mental Hygiene.

To summarize this survey of the problem of adaptation, we can say that adaptation of the individual to his ever-changing environment involves in the first place simple reflex action, as far as minor physical changes are concerned; but instinctive reactions modified by intelligence and character are involved when adaptation rises to the dignity of human conduct. In short, when adaptation reaches this dignity, the factors of the equation are: on one side, *individuality,* including *personality, temperament* and *character;* and on the other, changing *environment.*

Having this rough equation of adaptation in mind, we are now ready to discuss the nature of those forms of maladaptation called the psychoneuroses.

Psychology of Maladaptation.—Maladaptation is partial or complete failure to adjust successfully to the responsibilities and opportunities of civilized life. It is a substitute for, and a modification of, successful adaptation. The tendency to maladaptation is normal—common to all mankind—and becomes a subject for reëducational attack, a medical problem, only when it rises in degree sufficiently to threaten or actually to affect well-being and success. Then it amounts to a threatened or actual psychosis or psychoneurosis. Inasmuch as reëducational therapy applies especially to psychoneuroses, and to psychoses largely, if not exclusively, as far as their superimposed psychoneurotic elements are concerned, only the psychoneurotic type of maladjustment will be considered here.

Psychoneurotic Maladjustment.—Only the immediate exciting cause of psychoneurotic maladjustment can be found in environment. Even then the cause almost invariably proves to be more specific, that is, it is not inherent in the *particular* change, but distinctly in the fact that there has been *change*—a change demanding adaptation. The source of the failure in adaptation can, however, be found in some exaggeration or some weakness of one or more of the elements constituting the normal individuality. This cause is to be found in an oversensitive temperament, usually combined with some relatively overactive instinct, or in some other imbalance within the equation of individuality. Thus, largely independent of gross environment, these maladaptations take place, the variety in each case being determined by the individuality of the patient.

Irrespective of type, all cases show a lack of adaptability to the common changes in environment. All show that common human tendency to "short-circuit" on the instinctive level, but they show it to an unusual degree. A break of integrity between the individual and the environment results, and instead of responding to a situation as a whole person, the unity is broken and the response tends to be a mere reaction, satisfying neither the instinctive demand nor the needs of the situation. Whether this break of integrity takes the neurasthenic, the psychasthenic or the hysterical form, depends on the individuality. The poor, substitute adaptations are those, in short, of an intelligent or non-suggestible, a pugnacious or timid, a selfish or altruistic individual. But whatever else he may be, he is always to some degree hypersensitive.

The specific and characteristic tendencies which constitute the psychoneurotic risk or liability are:

Oversensitiveness to Emotions and Sensations.—The primary basis is a temperamental predisposition to over-respond to their pleasurable and painful elements; the secondary basis, poor training and discipline, allowing this predisposition to become habitual in action.

Relative Unbalance of Instincts.—For instance (and most commonly), the basis is a relatively overactive instinct of self-preservation, with a consequent prominence of fear and anger; the secondary element is misapprehension of the significance of these emotions, and therefore an exaggeration both of their affective and physical elements. In short, it is this instinctive unbalance which makes the general temperamental sensitiveness specific—to fear or anger, for example.

Suggestibility.—When suggestibility is combined with an inherent, probably inherited, tendency to dissociation of function: this, secondarily accentuated by wrong training, results in maladaptation of the hysterical type.

Character Faults.—These are usually a lack of training and discipline, with a consequently imperfect connection between ideals and performance, which results in an egotistic type of maladaptation.

Environment.—Lastly, the environmental conditions may be so terrifically hard, both socially and physically, as to defy the normal power of adaptation.

In General.—The psychoneurotic adaptation shows a more or less extreme tendency to "short-circuit" on the lower instinctive level. The individuality does not respond as a whole, but reacts only in part, showing a break in the integration of character in its response to life. A tendency to overmobilization of energy, a dead level of intensity of effort irrespective of need, is the commonest form of inefficiency exhibited by all types.

It is to be noted that all of these characteristics are found in the perfectly normal individuality. It is only when they become exaggerated or relatively unbalanced that they constitute psychoneurotic tendencies.

It must be added that usually cases do not fit definitely into any one class, but seem to belong to several, and we must be satisfied to label them according to their most predominant characteristics. This is to be expected when one considers of what complex and variable factors individuality is composed, and when one realizes that it, more than any other element, determines the type of syndrome. A diagnosis based on etiology in these cases is then obviously more helpful, as it deals directly with the individualistic peculiarities, which are both the guide of therapeutics as well as its objective.

The psychoneurotic liability also expresses itself in more general terms. It is a make-up which tends to go to extremes—to work at terrific speed and then to collapse; to like or to dislike extremely; to be conscious of self in terms of sensations and emotions rather than in terms of purpose, plan and ability; to be conscious of the world in terms rather of how it affects its possessor than how he may affect it. Besides the tendency to short-circuit on the instinctive, because he overvalues emotion and sensation, he tends, on the basis of this overvaluation, to mistranslate their significance and draws broad, general far-reaching conclusions—especially that he is fundamentally inadequate and cannot be expected to contribute a full share of effort. Many of these theories of inadequacy are part of a mechanism of escape. If a person *cannot,* he obviously escapes the responsibility of *trying* and the stigma of saying "I won't."

The expression of the instinct of escape, however, takes other forms besides this rationalization. The short circuit may be hysterical; or it may be merely emotional, as in a child who gets angry at his non-success and swiftly and violently transfers his anger to the recalitrant toy or person, working off his temper in an explosive, pugnacious and abusive way. The paths of escape are many. The child who tries abnormally hard for an abnormally high position and reputation for perfection is escaping the pain of criticism and blame to which he is abnormally sensitive. Or this same escape may be effected by deception or by aggression, the latter being akin to the blusterings of a frightened man.

Psychoneurotic Assets.—On the other hand, there are assets to offset the liabilities of the psychoneurotic tendencies. First on the list is sensitiveness. This, though it is so often the basis of maladaptation, is not in itself necessarily harmful or useless. It is a valuable risk. It is, as a matter of fact, a quality which, if understood by its possessor and valued in terms of its usefulness, may and should become one of his chief assets. Combined with clear purpose and intelligence, it constitutes one of the outstanding characteristics of the most useful and the greatest citizens of the world. Not all hypersensitive people break down; but it is those whose training and other environmental influences combine with ignorance to sidetrack them who suffer breakdowns. The others are those from among whom we choose our leaders. Combined with intelligence, this hypersensitiveness places one more quickly and completely "in touch" with any situation involving others. It makes, so combined, for greater appreciation and intellectual ability, greater finesse and success in adaptation. It is a two-edged weapon, but its possessor *need* not turn its edges on himself.

With hypersensitiveness, there usually goes increased imaginative power—surely an asset where it is controlled by intelligence and good purpose and a liability only if allowed to run wild.

In short, those having the tendencies which constitute the psychoneurotic liability also possess, in those same tendencies, potential assets far above the average. They are included in that invaluable group designated by William James as the "tender minded."

To return those among them, who have broken down, to full usefulness, to help them in their struggle, is a task worthy of no end of effort, and one who undertakes it must realize their worth, or, through his ignorant prejudice, he will fail.

Object of Reëducation.—It is particularly important to keep the main object of the reëducational method clearly in mind throughout its application. This object is the restoration to full usefulness, to a world which needs them, of people who are only temporarily disabled. A most essential and integral part of this object is *permanency of cure*—in short, the prevention of future "breakdown." To see that this result is not only possible, but is the immediate and direct object of every item of the treatment, has obvious suggestive value. Moreover, it gives a vital interest to even the dullest detail, and helps to keep the morale of both patient and physician at an effectively high level. Reëducation must not aim only at the restoration of functions, but must try strongly, constantly and particularly to revivify normal ideals; for the whole structure of mental and physical training would collapse without its object of normal, serviceable life.

The Means.—The instrument that this method uses is the patient's own intelligence, his own critical faculties, his educability. The material it gives this instrument to work on is knowledge—knowledge of its own nature and capabilities, understanding of its tendencies to bungle, and familiar comprehension of the technic necessary for the successful application of this knowledge to the problem of adaptation.

Method.—The first step in therapeusis is taking the patient's history. As has been said in a foregoing section, this process is beneficial or harmful to the patient, from the point of view of suggestion, according to how it is done. This fact is mentioned again, as its importance cannot be overemphasized. Furthermore, history-taking in cases particularly suitable for reëducational treatment is especially important, since much invaluable diagnostic evidence may be obtained in regard to the patient's inherent personality trends, habitual reactions, personal traditions, and temperamental quality. Every item of this sort is a therapeutic guide as well as a diagnostic aid.

Exactly the same may be said of the physical and neurological examination. It is of suggestive value or harm according to the technic, and is also of diagnostic value beyond that of the gross physical findings, for during its progress one may obtain valuable diagnostic hints as to the patient's individualistic reactions and characteristics.

Both of these preliminary procedures are, or may be, of reëducational value as well, provided the physician keeps this possibility before his mind and takes the trouble to explain the purposes of the various procedures according to their reëducational value.

In making a diagnosis, one cannot be satisfied with that form of "begging the question" which is called a "diagnosis by exclusion." There is always a reason, a sufficient cause for a psychoneurotic disorder, and the diagnosis does not exist as such until that cause, whether it be largely situational, largely personal or a "little of both," be found. Furthermore, a diagnosis should not be accepted as complete, or even sufficiently specific effectively to guide reëducation, until at least a good beginning has been made in the matter of estimating the patient's instinctive make-up—his temperament, his degree of suggestibility, his grade of intelligence and his degree of education and cultivation. This defining of the diagnosis must be done with great care, tentatively at first, very open-mindedly, for there is danger of trying to fit all patients into arbitrary classes too quickly and too much as a matter of routine. In this sense, the diagnosis may be allowed to develop toward completion as the case progresses, while the physician must guard it against his own prejudices, personal traditions and feeling.

Technic.—The first obstacle which reëducation meets, and the one which severely tests the physician's technic, is prejudice—prejudice on the part of the patient against his own difficulty. In this he only shares a popular idea which may be formulated somewhat as follows: "People, if they are sick, have something the matter with them; that something must be a physical disease or deformity, else it is nothing. If, therefore, a person is sick and has nothing physical the matter with him, he is just fooling himself, or he is enjoying a make-believe sickness." Nine times out of ten the patient will already have been told by otherwise perfectly competent physicians, "There's nothing the matter with you." They may even have added to this dictum, "You just imagine you're sick. Forget it." The patient, on the other hand, knows, is convinced, that he is sick. Likewise his self-respect necessitates rejecting the hypothesis that he is just a silly fool, or that he is merely amusing himself. He knows that he is "not that kind of an ass," and so goes on to seek further advice, hoping for relief, not only from his suffering, but also from the intolerable allegation that he is a silly or unethical malingerer. So it becomes a task of the first importance to remove this obstinate prejudice, by replacing the ignorance upon which it is founded, by knowledge of the *reality, respectability,* as well as the permanent curability of his type of disorder. The patient should be assured that he is in no way an object of scorn or ridicule, but, quite to the contrary, is in excellent company;

that, indeed, the very sensitiveness which has caused him inadvertently to break down can be made one of his greatest assets, as is the case in all the people he considers great. Naturally, to overcome this prejudice in the patient, the physician must be free from it himself. The man who is ignorant of the problem of adaptation, and is blinded by prejudice to the fact that the psychoneurotic difficulties are the same as his own—different only in degree—is fitted neither by knowledge nor by personal attributes to undertake this form of therapy.

Having made at least a beginning of destroying obstructive prejudice, the next step is to explain to the patient the object of the treatment, the rationale of the method, and to give him an outline, in some detail, of the various steps to be followed. The physician's relation to him may be described as partly that of teacher, partly of trainer, he being part pupil and part athlete.

The object—full restoration to usefulness, ability to progress toward the realization in action of his ideals—cannot be too clearly nor too forcibly nor too frequently emphasized.

Process.—The process itself of reëducation is fundamentally that of teaching, imparting information, and should first cover the general field of psychology, that is, normal man's adaptation, in a form suitable to the social and educational status of the individual. Sensory-motor mechanism, instinctive reactions, and intelligence in terms of judgment and choice, with the rôle each plays in adaptation, are some of the most important and useful items of general psychology to be taught. This part of the subject, if taught in language and with illustrations and analogies suitable to the social and educational status of the patient, may be made both interesting and stimulating. Next, the subject of maladaptation, with plentiful examples from everyday normal life, may be dealt with.

It is best to treat the subject thus far from an entirely impersonal point of view, simply as knowledge, valuable to any one, although the patient inevitably tends to make personal applications as he progresses. This does no harm. Rather it does good, for often a person will himself apply a truth to himself in a way which he would bitterly resent from another.

A consideration of ideals, their importance in the problem of adaptation, the common difficulties of their realization—again as a largely impersonal subject—is the last, very important part of the first, general phase of reëducation.

The next stage is that of aiding the patient to apply the general knowledge, just acquired, to his own specific difficulties. In short, it might be called the stage of personally applied Mental Hygiene. Aid, not only in understanding his specific difficulties of adaptation, but in applying this understanding to his daily thinking and doing, is now the main effort. This twofold object may be accomplished, first, by helping the patient to find himself in terms of personality and temperament, and to understand his disorder in terms of the tendencies which produced it, as well as in terms of the gross type of maladaptation which it, as a finished product, exhibits.

Secondly, aid in the application of this comprehension to everyday doing and thinking is made more effective by means of a well-planned day. The schedule for such a day should fit the patient's physical as well as mental state, and should contain work, play and rest in definite, predetermined quantities, each in proper relation and proportion to the other. The items of such a schedule can then be used as points of practice as well as object lessons in the failure or success of the patient's technic in adaptation. Such a schedule provides immediate, practical experience, giving opportunity for constructive criticism and tactful encouragement on the part of the physician.

Occupational therapy is here of great value. It offers opportunity for constructive work, objective action resulting in concrete achievement, which may be made the basis of returning self-confidence. Besides, it is incidentally a great help in using, to their advantage, the emotional energy of the overmobilized. It furthermore offers opportunities for teaching efficiency in the use of energies and for actually demonstrating, more easily and more clearly than could any purely didactic method, how this may be attained. Occupational therapy, however, would lose half its efficacy were its objective and its relationship to the rest of the treatment not fully comprehended by the patient. It is an important aid to reëducation; indeed, it is a very part of it, and should be treated as such.

Suggestion has already been dealt with in a foregoing section, but it must be mentioned here as a part, and an invaluable part, of reëducation. Formal direct suggestion, with hypnosis, is to be used only with highly suggestible patients for the removal of some hysterical disorder which obstructs their progress. Indirect suggestion, however, should be used all the time with all cases, as an element modifying the efficacy of each item of the treatment, from taking the history to the final discharge.

Adjuvant Agents.—It is necessary here only to mention the items of physical hygiene which obviously aid the patient's progress from disability to full usefulness, for it goes without saying that all such means should be applied, not just for their suggestive value but because there is almost always some secondary disturbance of the vegetative mechanism and frequently intercurrent physical disorders in the course of a psychoneurosis which call for correction. These secondary disorders may even be of a nature and a degree of severity capable of completely obstructing the progress of recovery. Therefore, due attention must be paid to the diet, the regulation of the bowels, the quantity of water ingested both at and between meals. The amount and type of exercise should be prescribed very definitely and corrective exercises given if they be indicated.

In short, the patient's physiological condition should be carefully studied, from the corrective, as well as the prophylactic point of view.

Continuation of Treatment.—As the object of this method is adaptation it cannot be attained away from home, away from all that to which the patient purposes to adapt himself. On the other hand, especially in severe cases, it is very difficult, if not impossible, to carry this method through successfully without removing the patient temporarily from his environment. It seems best, therefore, that a sufficient time be given up exclusively to reëducation and retraining—that the first stage of reeducation be considered a "going away to school" and be made an absolutely objective and, for the time being, an exclusive business. After the requisite knowledge has been acquired, and practice in application sufficient to clinch that knowledge, then the second stage of reëducation, namely, application at home, is in order. It is perhaps the most important part of the whole treatment, for it constitutes the final test of its efficacy and the first step toward permanency. It is, therefore, extremely important that a definite, even though long-distance, oversight be maintained, so that the patient may be advised, his application corrected, his successes consolidated, his failures explained as he progresses. It is often wise to arrange definitely for a return visit, a supplementary treatment, to take place a few weeks or a few months after the primary reëducation has been accomplished. A short review in the light of the patient's recent experience on such a trial trip is often most effective in driving home the most important points of his recently acquired reëducation.

Not infrequently the physician who deals with these maladaptations finds that to complete his work he must act as industrial adviser to his patient and sometimes even as employment agent. Indeed, like an old-fashioned "family physician," there are few jobs which he must not be ready and willing to include as a matter of course among his services.

From the very first contact, the main object must be kept in view—restoration to usefulness. It must be constantly in view throughout the active stage of reëducation, and finally it must be kept equally clearly in view during the final phases of home application. In short, it must never be lost sight of, either by patient or physician, until it has been *attained.*

CHAPTER II

PRINCIPLES OF SPECIFIC THERAPY

Ernest E. Irons

IMMUNITY

Chemical Nature of.—Whenever the physiological processes of the body are interfered with, whether by the invasion of microörganisms, or from some other physical or chemical cause, there results a series of physical and chemical changes not present before, which we call disease. These new changes are the outcome of chemical and physical rearrangements which must follow on the introduction of new substances into the system of substances previously in physiological equilibrium. The natural tendency of disturbed physiological processes is to return to normal, and so in the vast majority of cases interference with the physicochemical processes of the body results in only a temporary disturbance of normal function. The return to normal function may, however, be delayed, and clinical experience and laboratory experiment teach that under some circumstances the return to normal function may be hastened by the giving of certain drugs, or by the application of physical agents, which act by rendering the cause of disturbance inert, or by stimulating the physiologic processes to more rapid action.

Development of.—The problem of recovery from infectious disease, or the development of immunity, may be conceived of as involving a series of readjustments of disturbed physicochemical processes, quite similar to those in non-infectious forms of disease. We have to deal, however, with two antagonistic groups of processes, those of the invading organism and those of the host. The outcome of the struggle between invader and host will depend on the resultant of these extremely complex and interrelated forces. Their adjustment is one of great delicacy, and seemingly unimportant factors may serve to sway the balance to one side or the other. The invading organism may exert its unfavorable action on the host by means of a soluble toxin in the one case, by toxic substances set free by its death in another, or perhaps by mechanically causing obstructions in vessels and thus interfering with the function of vital organs.

Specific Defense of Host.—The host, on his side, protects himself by the elaboration of antitoxin to neutralize toxin, of substances which act injuriously on the invader, bacteriolysins, or by the engulfing and digestion of bacteria by migratory cells of the body. As in the non-infectious disturbances of physiological equilibrium, the reactions of the body tend to readjustment by the elimination of abnormal substances; expressed clinically, infections tend to result in immunity. The formation of defensive substances is to a large extent specific for each organism; the antitoxin formed to defend the body against diphtheria toxin will neutralize only diphtheria toxin; tetanus antitoxin will neutralize only tetanus toxin. Blood which is bactericidal for typhoid bacilli may have no effect on plague bacilli. The specificness of the defense complicates the study of immunity, but need not preclude the conception of it as a chemical process; as will be seen later, the specificity of antibodies argues for an adjustment of chemical structure of a particularly fine nature, not recognizable by the ordinary methods of clinical examination at our command. In recent years attention has been directed to the consideration of reactions which are less clearly specific, and concern the general problem of inflammation rather than the special invading organism.

Specific Therapy.—Specific therapy aims to assist the natural forces of the body in their struggle with the invading organism, either by supplying substances which shall neutralize the poisons of the invader (antitoxin), or by stimulating cells of the body not engaged in the struggle, to reënforce by the formation of various antibodies the efforts of those cells already involved in a local infection. Specific therapy also is concerned with the application of certain drugs, either in their natural forms or combined in organic compounds, which shall act injuriously on the invading organism, at the same time leaving the cells of the host unharmed. Mercury and quinin are commonly cited examples of the former class; arsphenamine, and other similar combinations of arsenic, of the latter. Thus far attempts at specific chemotherapy have been successful for the most part in the treatment of non-bacterial infections, such as those due to trypanosomes or spirochetes. Studies in vital staining, in which various dyestuffs are found to combine with bacteria, giving reactions dependent on the chemical constitution of the cell substance, are suggestive of the possibilities of chemotherapy.

Immunological Reactions as Physicochemical Processes.—Studies of the disturbances of normal equilibrium which take place in the tissues and fluids of the body in response to the introduction of foreign substances of bacterial or other protein nature have resulted in the discovery of an immense number of facts, and the demonstration of a number of properties of normal and immune serum which constitute the data of immunology. The further discovery of new facts and reactions has been facilitated by the grouping of facts already known into systems and theories, such, for example, as the side chain theory of Ehrlich and the ferment theory of Abderhalden. In the explanation of immunological processes and reactions, chemical conceptions have occupied an increasingly prominent place, and it has become evident that in studies on antibodies we are dealing with the same classes of chemical substances, with which the physiologic chemist experiments, and, further, that the resultant reactions are governed by the same physicochemical laws of osmosis, electrolytic dissociation, mass action, surface tension, temperature, and concentration. The extreme delicacy and high degree of specificity of biological reactions place them in a position of isolation from other groups of chemical reactions, but the gulf which years ago appeared too wide and deep ever to be bridged is now spanned by many connecting theories supported by well-established facts.

If, for example, we study the agglutination of bacteria by immune serum, which action we attribute to the presence of antibodies, called from their action agglutinins, we are at once met with the fact that this process of agglutination requires the presence of electrolytes, that its rate is influenced by temperature, concentration of bacteria and of serum. We further find that agglutination specific for one group of bacteria is a property not entirely unique to immune serum. A similar specificity of agglutination may be obtained with dilute mineral acids, and the specificity may be varied for different groups of bacteria by varying the concentration of the acid solutions. Other similar examples present themselves in the study of precipitins.

The colloidal gold reaction of Lange is a familiar example of the relation of physicochemical conditions to the reactions of albumins under varying clinical conditions.

Zsigmondy found that certain albuminous bodies when brought in contact with a solution of colloidal gold in the presence of an electrolyte would in certain concentrations cause a clumping together of the small colloidal particles, with a resulting change in color of the solution and later precipitation of the particles of gold. This precipitation was prevented if the concentration of the albumin was increased. The degree of concentration at which precipitation ceased and protection began was different for each albumin. Lange applied these facts to the examination of cerebrospinal fluids and found that by making a suitable series of dilutions of the fluids, color reactions may be obtained with the colloidal gold, sufficiently constant in different dilutions in different diseases to allow of the utilization of the reaction in diagnosis. Thus the concentrations of the fluid at which color changes or precipitation occurs in fluid from cases of tabes differ from those giving reactions when fluid from suppurative meningitis is used. Quite apart from the question of the reliability of the test as a diagnostic procedure, the phenomenon affords a striking demonstration of the chemical nature of changes in fluids of the body in response to different kinds of infection. As might be expected, any deviation, however slight, from the prescribed method of preparation of reagents interferes with the physicochemical conditions of the reaction and results in discordant reactions.

Chemical Nature of Antigens.—The structural and physical relations of the substances which have antigenic properties (that is, are able to stimulate the production of specific antibodies when introduced into the living animal) are of interest, not only from the point of scientific research, but by reason of the direct bearing of the question on problems of therapy. None of the substances, the exact chemical structure of which is known, possesses true antigenic properties, although it is possible that certain poisons, for example, whose chemical structure is known, may combine with albumin by a process of adsorption to form substances having specific antigenic powers, as evidenced by the formation of antibodies for these poisons or their combinations (Pick). In general the presence of protein in a substance is essential to antigenic power. The number of the antibodies produced by antigens probably varies with the size of the antigen molecule. Thus diphtheria toxin produces only antitoxin, and may be regarded as monovalent in distinction from polyvalent albumins which give rise to a number of immune bodies, such as agglutinins, precipitins, and lysins in the same serum. The valence of an antigen appears to be closely associated with the size of its molecule, as shown by the relatively more rapid diffusion of monovalent antigens, such as diphtheria toxin or cobra toxin through osmotic membranes, as compared with polyvalent antigens. The alteration of albumin by splitting it into simpler substances changes its antigenic qualities and eventually destroys them entirely.

The reactions of antigens and their antibodies present in many respects a close analogy to the reactions of other colloidal substances. Both are influenced by physicochemical conditions, such as the degree of acidity or alkalinity of the menstruum, relative solubilities and concentration, electrical charge, temperature, and surface tension.

Landsteiner has divided the reactions of immunity into two groups, the first of which comprises those involving the simple union of two colloids, as exemplified in agglutination, precipitation, and the neutralization of toxin by antitoxin; the second of which includes those reactions involving the solution or destruction of cell membranes through the action of colloids (antibodies) on the lipoid-albumin combination of the membranes. Examples of this latter class of reactions are the phenomena of hemolysis and bacteriolysis.

Further, the antigenic qualities of an albumin may be modified by physicochemical means, such as the application of heat, or exposure to various chemicals, such as acids, chloroform, toluol, or metals, as iron, lead, and mercury. This treatment need not result in the complete alteration of the albumin molecule, but may affect only certain groups. If rabbit serum is treated with concentrated nitric acid and the resulting nitro-albumin (xanthoprotein) used for immunizing the rabbit, an immune serum is obtained which will precipitate not only the rabbit nitroprotein, but also nitroproteins prepared from other foreign albumins. If foreign nitroprotein is used for immunization, the resulting immune serum will precipitate the corresponding and other foreign nitroprotein similarly to the serum obtained from the homologous serum antigen. Both sera show relatively little specific precipitating power with respect to the corresponding albumins from which the nitroproteins were obtained (Pick). This loss of antigenic power with respect to the specific albumins and the gain of antigenic power for nitroproteins, in general, are regarded as additional evidence that the quality of specificity resides in the slight variations in side groups attached to the central albumin molecule, and that by substituting one group for another the specific antigenic qualities of an albumin may be modified.

The possibility of altering specifically the antigenic qualities of a protein furnishes another means of approach to the problem of immunization against disease. It has long been known that if erythrocytes of a given species are saturated with a corresponding hemolytic immune serum they lose the power of stimulating the production of hemolytic antibodies when injected into a foreign species. This loss of antigenic power has been explained on the supposition that the specific groups of the erythrocytes have been occupied by antibodies of the immune serum, and are no longer able to unite with receptors of the cells of the animal into which they are introduced and hence do not stimulate the further formation of these antibodies.

Bacteria treated with corresponding immune sera appear to be less toxic for animals than untreated bacteria, and some observers have noted a decrease in the antigenic power of the treated bacteria for the production of agglutinins and precipitins, with an increase in the production of bactericidal substances.

Relation of Host to Invading Organism.—The formulation of a rational treatment of an infectious disease requires in the first place a knowledge of the nature of the infecting organism. Gradually the lines of differentiation of the infections have been more clearly defined, so that the entity of many, such as diphtheria, typhoid fever, epidemic meningitis, cholera, plague, has been established, and the specific organism causing them discovered. Other diseases, such as the acute exanthemata, are fairly well defined clinically, but we know but little of their etiology beyond the presumptive evidence that they are caused by some form of living organism.

The discovery of the causative organism of a disease does not, however, solve the problem of its specific therapy, and is only the first step toward the determination of the sequence and relation of chemical processes and reactions by which the symptoms of the disease are brought about, and by which the disturbed physiological equilibrium is returned to normal.

These processes concern those of the offense of the invading organism and those of the defense and offense of the host. Recently more attention has been given to the changes in the invading organism by which it may increase its defense against the counterattack of the host.

Defense of Host—*Antibodies.*—Among the most readily demonstrable changes which occur in an animal in response to invasion by a microorganism are the new properties acquired by the blood serum, which are indicated by the names, antitoxin, agglutinin, precipitin, bacteriolysin, opsonin, descriptive of the nature of their several actions. Much has been learned of the nature of these antibodies to bacteria and their products by a study of the antibodies produced in response to the inoculation of other foreign cells and proteins, by which hemolysins, cytotoxins, or precipitins are formed. It is important to bear in mind that we recognize antibodies in sera to a large extent by the physical changes which they produce in cells or fluids to which they are added; that, so far as we know, the number of classes of recognized antibodies is limited only by the number of methods which have been devised for their demonstration, and that, while they exhibit a degree of specific action not attained by other chemical processes, this specificity does not argue against the basic physicochemical action of antibodies, but rather for a particularly fine adjustment of chemical structure. The introduction of an antigen is the most efficient, and usually the only, method we possess of producing other substances (antibodies) which shall meet exactly the physicochemical conditions necessary for union with the antigen.

Ehrlich's Theory.—From time to time theories have been evolved based on generalizations from groups of facts observed in relation to the changes produced in animals by the introduction of foreign protein. Perhaps the theory most useful in promoting investigation in immunity has been that developed by Ehrlich. This receptor or lateral chain theory was first formulated to explain the assimilation of food by cells and later was expanded to cover the production and action and standardization of diphtheria antitoxin. The theory has been widely employed in the classification and explanation of other reactions of immunity, so that the terminology of the subject of immunity is largely that of the side-chain theory. The theory, already familiar to all, is based on the supposed analogy between the products of the cell and complex chemical substances, such as those containing the benzin ring, the special chemical properties of which are determined by the attached side groups or radicals. It assumes that the cell possesses certain groups or receptors capable of combining with foreign substances, and that, when these receptors are occupied by the combining or haptophore groups of the foreign substance (antigen), new receptors are formed by the cell. Following Weigert's law of overcompensation in regeneration, an excess of receptors is formed and cast off into the blood. These cast-off receptors constitute the antibodies. The great excess of free receptors produced in response to some types of immunization, as, for instance, in antitoxin formation, has been explained by some on the theory of stimulation of the cells by the toxin, rather than by the more limited action of Weigert's principle of overcompensation.

Ehrlich has divided antibodies into groups according to their mode of action. In the first order he placed the antitoxins, which possess one combining group—that for the toxin molecule. In the second order are those antibodies which possess a combining group for the antigen and an "ergophoric" group, by which the antibody exerts its characteristic action on the antigen, for example, agglutinins, precipitins. The third order of antibodies includes those which possess two combining groups, one for the antigen, and one for a third substance complement, which is the active agent in promoting changes in the antigen, for example, lysins, bacteriolysins. Antibodies of this class thus serve to bring together, or make possible, a reaction between antigen and the third substance (complement), and hence have been termed amboceptors.

Objections have been raised to the lateral chain theory of Ehrlich on the ground that it presupposes an unnecessarily complicated system, and that the terminology is cumbrous. If, however, each term of the theory is conceived of as descriptive of a combination of physical conditions and chemical structure, which, when reproduced under constant conditions, may be depended on to react in a constant manner, specificity in this sense is seen to be as much a chemical property as the reactions of precipitation of metals and salts in inorganic chemistry; and the complicated terminology is merely an expression of the exacting conditions under which the reactions of immunity take place. The terminology has been unnecessarily complicated by the introduction of several terms for the same substance or idea. Thus, for instance, immune body, amboceptor, preparator, fixateur, substance sensibilisatrice, have been used by various workers to designate the same property in immune serum.

Mass Action in Passive Immunity.—The conceptions of Ehrlich in regard to certain of the fundamental facts of the reactions of antigen and antibody have not been accepted in their entirety by other workers. For example, Ehrlich held that the union of toxin and antitoxin is an irreversible reaction, while Arrhenius and Madsen contended that the process is governed by laws of mass action, and that accordingly in a theoretically neutral mixture of toxin and antitoxin there is always a small amount of free toxin present. In the presence of an excess of antitoxin the amount of free toxin grows smaller. Experiments with osmotic membranes indicate that the latter view is more nearly correct, and that diphtheria toxin may be separated from antitoxin with which it has united, although the process of separation is very slow.

Importance of Large Doses of Antitoxin.—The application of the laws of mass action to the union of toxin and antitoxin is of practical importance in the treatment of such diseases as diphtheria and tetanus. When the patient comes under treatment he has more or less free toxin circulating in the blood, and it is essential that as much as possible of this toxin shall be immediately neutralized and prevented from becoming fixed in vulnerable tissue cells. To accomplish this, large initial doses of antitoxin will be more effective than smaller doses, even though the latter might be just sufficient to neutralize all the toxin present. In some urgent cases of diphtheria and in all cases of tetanus, to be of full value in saving life, the antitoxin must reach the blood more rapidly than is possible by the slow absorption from subcutaneous tissues which only reaches the maximum after forty-eight to seventy-two hours, and the intravenous injection offers a rapid means to this end.

Duration of Passive and Active Immunity.—The relatively short duration of passive immunity acquired by the introduction of an immune serum, as compared with the more lasting active immunity obtained by the direct inoculation of toxins or other antigens, is generally recognized, but the importance of distinguishing between the two types is so great that a reference to the subject seems warranted.

In general, when diphtheria antitoxin or tetanus antitoxin is given subcutaneously, the amount of antitoxin in the blood increases gradually, reaching its height about forty-eight to seventy-two hours after the injection, and then decreases slowly until at the end of ten days or two weeks very little is left in the blood. If the antitoxin is given intravenously the concentration of antitoxin in the blood reaches the maximum much earlier, and then slowly decreases at about the same rate as when given subcutaneously. Clinically, protection, so far as it is derived from the one injection of tetanus antitoxin, ceases after the third week.

Antibodies derived from homologous sera disappear more slowly than those from alien sera. Thus in experiments reported by Lüdke and Orndschiew the agglutination titer of the blood of rabbits for dysentery bacilli rises rapidly after the subcutaneous or intravenous injection of specific immune goat serum of high agglutinating titer, and then falls rapidly, and at the end of eight days reaches the level of agglutinative power present before the injection of the serum. If, however, immune rabbit serum is used for the injection of rabbits the titer rises rapidly as before, but falls more slowly, reaching its normal level only after twenty to thirty days. Similar results were obtained in man, using goat and human sera agglutinative for typhoid bacilli. Agglutinins derived from goat serum disappeared usually by the sixth day, while agglutinins derived from highly immune human serum were still demonstrable on the fourteenth day.

These experiments were made with serum containing no appreciable trace of the specific antigen used in their production. Where immune goat serum containing a small amount of antigen was injected into rabbits or man, the agglutinins remained high for longer periods and were still present at the last examinations made, thirty days after injection. These results conform to those of earlier workers. Theobald Smith conducted a series of experiments based on the fact that the offspring of female guinea pigs immunized to diphtheria toxin inherit a demonstrable antitoxic immunity. He showed that mixtures of antitoxin and toxin in which the antitoxin is present in great excess produce relatively little or no lasting immunity, but that as the proportion of toxin increases the immunity becomes more lasting, and that by the injection of suitable toxin-antitoxin mixtures which have no harmful effects, either immediate or remote, an active immunity lasting several years can be produced in guinea pigs. Therefore this combination of passive and active immunization has found an important application in the prophylaxis of diphtheria.

In general, the duration of passive immunity is limited to days or weeks. Active immunity, on the other hand, may last for months, years, or even for life. Much seems to depend on the degree of thoroughness with which the body is sensitized, recovery from a mild attack of the disease being the most efficient method of sensitization. Some diseases such as pneumonia, erysipelas, and gonorrhea apparently confer an immunity which persists for a relatively short period. However, it appears that in pneumonia, at least, the immunity produced is referable to a large extent to the specific strain of pneumococcus concerned in the attack, and that subsequent attacks may be caused by unrelated strains.

Other Protective Mechanisms of Body.—The theories of immunity most extensively applied thus far in researches into the mechanism of immunity have been those related to changes in the serum, antibodies and ferments, believed to be derived from fixed or mobile cells in response to the stimulation of the infecting organism, and those which have to do with increase of phagocytic activity of leukocytes and other cells, acting alone or by the assistance of serum containing opsonin.

In addition to these, a number of other derivatives of body cells have been found to have definite bactericidal action. Leukocytes yield substances which are thermostable and bactericidal. Hiss and Zinsser found that extracts prepared from the leukocytes obtained from rabbits following the intrapleural aleuronat injections were able to modify the course of pneumococcus, staphylococcus, meningococcus, typhoid, and cholera infections in animals, and that in many cases the animals were saved from an otherwise fatal dose. These authors believed also that lobar pneumonia, erysipelas, and cerebrospinal meningitis in man could be favorably influenced by the inoculation of such extracts.

Opie found that otherwise fatal experimental intrapleural tuberculous infections in dogs could be made to heal by the introduction of living dog leukocytes, and Manwaring noted a similar protective influence of leukocytes in experimental tuberculous meningitis of dogs. It is believed that certain of these non-specific protective substances may act as ferments; other substances such as the soaps of fatty acids may act indirectly on the invading organism by modifying its chemical relations to other protective substances or cells.

The production of the toxic phenomena of disease by the non-specific derivatives of the proteolysis of bacterial cells in diseases such as typhoid fever may be cited as an instance of how reactions which are primarily protective may become antagonistic to the life of the host. Kolaczek and others have urged further that the general symptoms such as fever, which accompany local abscess formation, are referable to the toxic action not only of the products of bacterial proteolysis, but also of proteolysis of dead tissues of the body, whose solution has been brought about by leukocytic ferments present in the abscess cavity. On the basis of the observation that albuminous fluids such as those of ascites or pleural effusion or blood serum itself are able to stop this proteolytic action in vitro, Kolaczek suggested the treatment of acute phlegmons and abscesses by the injection of such albuminous fluids. The favorable results which have been observed from this treatment in the decrease of symptoms of general intoxication and local destruction of tissue may be due in part to the so-called "antiferment" action of the serum, but there must also be taken into account the effect of relief of tension in the abscess which follows the puncture and evacuation of the contents of the abscess, as well as the possible action of fresh leukocytes, opsonin, and amboceptors, introduced in the serum.

THE INVADING ORGANISM

In general we may designate a microörganism infectious if it is able to multiply and produce symptoms of disease in the animal body. In order to produce disease it must enter the body, and in doing so must overcome obstacles, some mechanical, others functional, of the cells and fluids of the host. The rapidity and extent of the invasion depend, in part, on the readiness with which the organism assumes a parasitic existence in the host, the site of entrance into the body, the size of the initial dose, and the resistance of the invader to the attack of the defensive forces of the host. When an organism has entered the body, the kind of tissue in which it produces clinically recognizable lesions is determined in part by chance, and in part by the growth requirements of the organism, such as available food supply, oxygen tension, and protection from the defensive fluids and cells of the host. Different tissues present different combinations of these factors. Some organisms are more likely to survive and multiply in one kind of tissue, others in another. Thus most osteomyelitis is staphylococcal in origin, while staphylococcal arthritis, except in overwhelming sepsis or in traumatic arthritis, is unusual. Streptococci are likely to survive and grow in serous membranes, including those of joints, and streptococcal arthritis is common, while primary streptococcal osteomyelitis is relatively unusual.

Organisms may come to occupy portions of the body relatively inaccessible to the defensive substances of the body. The recognition of this latter factor is of great importance in devising and applying therapeutic measures. Thus antimeningococcic serum is unable to bring about the cure of epidemic meningitis if injected subcutaneously, but if introduced into the blood and into the subarachnoid space by lumbar puncture has a prompt effect in promoting the phagocytosis and solution of meningococci, and assists in the cure of the disease.

Virulence and Serum-fastness.—*"Serum-fastness"* of organisms by which they become relatively insusceptible to the destructive action of immune sera and phagocytes has been partially explained in various ways. Some degree of serum-fastness is probably a component of the initial virulence by which an organism gains a foothold in the body; the presence of a capsule or relative increase in thickness of the ectoplasm are sometimes noted in virulent strains and in those recently isolated from lesions in animals, and have been regarded as the means by which the resistance of some organisms is increased. Virulent bacteria may differ from the avirulent by the presence within or about them of substances which act either as direct physicochemical repellants to the leukocytes (negative chemotaxis), or may interfere with the specific opsonic action of serum, and so prevent phagocytosis. Thus Rosenow, in a study of virulent pneumococci, attributed their resistance to phagocytosis to the presence of a substance which he termed "virulin"; after the extraction of this substance, previously resistant pneumococci became phagocytable, and avirulent readily phagocytable pneumococci when treated with "virulin" became resistant to phagocytosis. The action of the aggressins of Bail (derived from the peritoneal exudate of animals inoculated with living bacteria) in increasing the power of a bacterial suspension to produce fatal infection in a second animal has been thought by some to be due to endotoxins and other bacterial products, which reënforce the toxic action of the inoculated bacteria; by others their action has been regarded as directed against the leukocytes.

Fastness may also be exhibited by organisms with respect to immune sera which are known to exercise bactericidal action. Flexner noted that in certain cases of epidemic meningitis which fail to respond to treatment with antimeningococcic serum there are indications that the organisms belong to strains relatively more resistant to the action of the serum. Serum-fast strains may also develop in the course of an infection, and the fatal relapses, following the initial improvement under serum, are thought to be sometimes caused by strains which have become more resistant to serum action. The occurrence of strains of meningococci in epidemic meningitis, different from those used in the preparation of the antimeningococcic serum employed in treatment, affords an explanation of what at first appeared to be a widespread type of acquired serum-fastness.

The well-known experiments of Ehrlich on infections by trypanosomes have demonstrated that acquired fastness is an important factor in chemotherapy and that exposure of organisms to the action of chemical substances of known formula may result in the appearance of strains with increased resistance to the special substance used.

The modifications exhibited by bacteria during their sojourn in the host are, however, no more striking than the changes in growth, resistance, and toxin formation in the culture tube in response to alterations in physical and chemical environment, but the acquisition of these new qualities within the host and the development of more resistant substrains during the course of a chronic infection further complicate the difficult problem of therapy.

SPECIFIC CHEMOSEROLOGIC THERAPY

The knowledge of the mechanism by which each microörganism protects itself against its host makes it possible to devise methods of overcoming this resistance, and already improvements in practical therapy have been made with this principle as a guide. Polyvalent antisera in which known resistant strains are included in the group of bacterial strains used in the production of the serum have been suggested to overcome the serum-fast strains of meningococci. Strains of trypanosomes, fast with respect to one chemical, have been overcome by the use of a second closely allied chemical.

The experiments on pneumococci described by Flexner illustrate at once the value of the conception of immunity as a problem of immunochemistry, and the importance of the adjustment of chemical relations to meet the known biologic peculiarities of the organism. The essential data of the experiment may be summarized as follows: A 1 per cent solution of a soap, such as sodium oleate, converts pneumococci into a viscid mass. Weaker solutions (0.1 per cent) do not kill the cocci, but they are more readily autolyzed after the treatment. After exposure to still weaker solutions (1:20,000) the pneumococci show no changes in form or staining power, and are able to grow in cultures. But they are more readily autolyzed, show increased susceptibility to the action of immune serum, and their virulence is somewhat lessened, although they are still able to produce septicemia in white rats.

If a series of rats are now inoculated the following general results (tabulated from Flexner's description) are obtained:

Rats inoculated with untreated pneumococci, death in 18 hours.
Rats inoculated with untreated pneumococci + immune serum, death.
Rats inoculated with soaped pneumococci, death in 30 hours.
Rats inoculated with soaped pneumococci + normal serum, death.
Rats inoculated with soaped pneumococci + immune serum, recovery (animals not ill).

The soap and serum together were thus able to accomplish what neither could do alone.

The application of oleate and immune serum as a treatment of established pneumococcic infections meets with a serious difficulty, however, in the fact that the lytic action of soaps of fatty acids is prevented by the protein substances in the serum, and it is necessary to add a third substance such as boric acid to protect the soap from the protein. Flexner has applied this combination of soap, boric acid, and serum to the treatment of experimental pneumococcal meningitis in monkeys and has succeeded in thus curing the disease, from which untreated animals regularly die. An immune serum corresponding to the special strain of pneumococcus used is necessary to the success of the method.

Morgenroth devised a successful chemotherapy of pneumococcic infections in mice by means of ethylhydrocuprein. The combination of immune serum with the ethylhydrocuprein is much more effective than either alone. The percentages of recoveries of mice from intraperitoneal infection with the pneumococcus show the results of the combination of the two methods of attack (Boehncke).

Untreated	recovery in 0 per cent.
Treated by chemical alone	recovery in 20 per cent.
Treated by immune serum	recovery in 33 per cent.
Treated by immune serum + chemical	recovery in 90 per cent.

A new field of usefulness is thus opened for specific immune sera, of which only a limited number have hitherto proved of unquestioned value in the treatment of the acute infections where their help is most needed. As Flexner suggests, an immune serum forms a very favorable basis on which to build up a specific chemical therapeutic agent, because the serum already has a structure suited to its union with the microörganism, and is also relatively innocuous for the cells and tissues of the host.

Serum utilized as the carrier of an active chemical not only may make the chemical more effective, but may serve the further purpose of protecting special cells and structures of the body from the injurious action of the chemical.

The search may be long, however, before the combination of immune serum and an active bactericidal radical is obtained, which will satisfy all the chemical conditions necessary that the remedy may sway unfailingly the balance of immunity against the invader. The problem involves chemical reactions of fine and intricate nature, and the solution for one disease may not be applicable to another disease having a closely related symptomatology. The mode of attack must be individualized for each disease, and may even have to be varied for stages of the same disease.

INFLUENCE OF ONE INFECTION ON ANOTHER

The chemical reactions involved in the struggle between the invading organism and the host are of an extremely intricate character, and the unstable balance between the two groups of forces may be swayed to one side or the other by many factors, some of which may be non-specific so far as we can tell from our present methods of determining specificity. The introduction into the subject of an infection of chemicals or cells which stimulate the production of leukocytes may suffice to influence the balance of the reaction toward recovery. The practical difficulty in the application of such vigorous and non-specific methods is met in the fact that the new element may swing the balance against the body as often as for it.

The experiments of Doerr show that the inoculation of bacteria or their toxins frequently renders animals much more susceptible to the invasion of other bacterial species subsequently introduced. The severe clinical course of multiple infections, by two or more organisms in the same individual, usually ascribed to the summation of the toxic effects of the organisms on the host, may be due to a coöperation of their combined ferments, or, speaking biologically, to a symbiosis, which enables them together to exert an aggressive action not possible for either alone. The secondary infections of tuberculous processes are instances of the unfavorable action of one infection superimposed on another. In the subjects of multiple infection or of pyogenic infections in several parts of the body, the favorable effects which sometimes follow the removal of one area of infection may result merely from a lightening of the total load, so that the resistant forces of the body are able to overcome the remaining infections.

Other combinations of diseases met with clinically offer examples in which the balance is deflected in favor of the host. Certain malignant tumors show a temporary arrest of growth, or even decrease in size during and immediately after an intercurrent infection such as erysipelas. While the etiology of malignant tumors is a matter of controversy, it is generally admitted that they present in their immunological relations to the host many similarities to infectious processes, and it is easy to see that the balance between the aggressive forces of the tumor and the resisting forces of the host may be profoundly influenced by the introduction into the combined systems of forces of a third group derived from the acute infection. The chronic granulomatous process known as Hodgkin's disease presents a similar recession of symptoms under the influence of an intercurrent infection.

NON-SPECIFIC INTOXICATION AS A CAUSE OF SYMPTOMS OF INFECTIOUS DISEASE

A number of problems arise in regard to the means by which the body rids itself of the infecting organism, and the part which this process of elimination plays in the production of the symptoms of disease. In the physiological process of gastro-intestinal digestion foodstuffs undergo successive stages of hydrolysis under the action of ferments, until they are resolved into substances sufficiently simple for absorption and assimilation. A similar process of splitting into simpler subtances is assumed to take place when foreign protein substances are introduced into the body by parenteral routes, and the toxicity of some of these products produces a complex of symptoms known as *anaphylaxis.*

Abderhalden extended his investigation of the relations of body cells and their specific ferments to the relations of the invading organism and the host. In order that the invading organism may gain a foothold and multiply in the host it must possess ferments by which it can break down the substances of the host into products sufficiently simple that they may be utilized in building up the bacterial protein. If the organism does not possess such ferments it cannot obtain the necessary food supply, and hence is incapable of multiplication. The cells of the host may neutralize or otherwise prevent the action of the ferments of the microörganism, and by this means the multiplication of the latter is prevented. Various drugs also may aid in the defense of the host by altering unfavorably the physical or chemical conditions of action of the ferment of the invader, or by changing the susceptibility of the fluids and tissues of the host to its action.

The host may suffer not only from the direct toxic action of the invader, but also from the possible toxic effects of the products of the proteolysis of his own tissues, brought about by the ferments of the invader. Finally the host suffers most severely from intoxication by the products of proteolysis of the foreign bacterial protein, induced by the ferments mobilized by the cells of the host in response to the stimulus of bacterial invasion. The identity and structure of the ferments of Abderhalden are as unknown as are those of the antibodies of Ehrlich, and we recognize their presence only by their effects on other substances. In studying the action of ferments, the physical and chemical changes in the substances on which they act, changes in rotation of polarized light and alteration of rate of diffusion through membranes replace the phenomena of hemolysis, agglutination, and precipitation employed in the study of antibodies.

The phenomena of sensitization and allergy were first studied in animals following repeated inoculations of alien sera, but the principles of immunization developed from these facts have found a wide application in relation to the disturbances which follow the introduction of bacterial protein into the animal body.

The toxic action of bacteria was formerly ascribed to endotoxins liberated by the dissolution of the bacteria cells in the body. While endotoxins may be present and give rise to some of the toxic effects of bacterial infection, the view has been advanced that the products of digestion of bacterial protein itself are responsible for many of the toxic effects on the animal body. Vaughan, Friedberger, and others showed that if a bacterial suspension is digested by chemical means, or by treatment with bacteriolytic sera, the toxicity of the suspension is enormously increased. The injection of suitable doses of these toxic products into normal animals produces symptoms of cutaneous irritation, respiratory embarrassment, hemorrhages, and death, identical with those produced by inoculations of the unaltered bacterial or other proteins into animals sensitized by a previous inoculation of the corresponding protein. This toxic substance has been called by Vaughan "protein poison," and by Friedberger "anaphylatoxin." The latter also showed that if the proteolytic digestion is allowed to continue after the period of maximum toxicity is reached the products become less and less toxic.

Other writers, following the lines suggested by the work of Bordet, have found that by mixing serum with kaolin, substances are produced equally as toxic as those derived from mixtures of serum and bacteria, and from these experiments have argued that the toxic substance is probably derived from proteolysis of the serum itself rather than from the bacteria.

Vaughan obtained a toxic substance from the cells of a number of bacterial species and also from vegetable proteins such as edestin and zein, which, in doses of .5 milligram given intravenously, was fatal to guinea pigs, and in non-fatal doses when given to guinea pigs produced a series of phenomena characterized by cutaneous irritation, urticaria, and later partial paralysis and also shallow rapid breathing, with a marked depression of temperature. Small doses of the poison given subcutaneously caused fever, as did also the unchanged proteins. By regulating the size and interval of doses of the poison various types of intermittent and continued fevers were produced. In those of the long-continued type progressive emaciation occurred. In man the protein poison caused general cutaneous hyperemia and urticaria.

The relation between host and invading organism may be re-stated in terms of nutrition and proteolysis. In order that the organism may gain a foothold and multiply it must be able to split and utilize the proteins of the host, and the host must not at the outset be able to destroy the organism (proteolysis, bacteriolysis). If either of these conditions is not fulfilled infection cannot occur.

After the infection has been present for a time the body of the host elaborates ferments (antibodies) which act specifically in limiting the growth and accomplishing the destruction of the invader. But after the invasion has been checked the host has still to dispose of the foreign bacterial protein, and it is the products of this parenteral digestion which are thought to give rise to the severe toxic symptoms of many infections.

Thus, according to Vaughan, during the incubation period of typhoid fever rapid multiplation of the bacilli is taking place and they are building up typhoid protein out of the tissues of the host, but there is no splitting of typhoid protein, and no symptoms of intoxication are evident. After a period of ten days the cells of the host are sufficiently stimulated to form specific ferments with which to break up the typhoid protein, and the protein poison begins to show its effect in the production of fever, headache, and prostration.

It may be added that at about this time the specific ferments (antibodies) of the host limit the further growth of the invader, and soon after the bacilli disappear from the blood. The course of typhoid fever may be regarded as consisting of two overlapping periods, the first concerned largely with the invasion, and later the limitation of growth, of the invading bacillus, on the one hand, and the sensitization of the host, on the other, and the second with the disposal of the foreign protein remaining after the invasion has been checked. An acceleration of the proteolytic process results in the liberation of excessive doses of the protein poison, with severe intoxication and perhaps death of the host. In this way forces otherwise protective become injurious to the defender.

This theory of the non-specific cause of the symptoms of intoxication in infectious diseases need not imply a non-specific defense on the part of the host. That part of the defense directed toward the limitation of growth and ultimate death of the invader still may be assumed to be specific. Also the ferments which break up the foreign protein may be specific for that particular organism, even though the products of their proteolytic action possess qualities in common with derivatives of other proteins. Nor does the acceptance of a non-specific protein intoxication as the cause of some symptoms exclude the possibility of the presence and action of specific toxins, though these may play a less important rôle than was formerly thought.

APPLICATION OF SPECIFIC BIOLOGIC METHODS TO TREATMENT OF INFECTIOUS DISEASES

The conception of infectious diseases, as involving reactions corresponding to those which take place in the chemical laboratory, has contributed largely to our present knowledge of the mechanism of recovery from infections, and to the development of methods of therapy. The extreme complexity of these chemical reactions, and their intimate relations with the cellular and humoral processes of the body, which themselves may be thought of as finely adjusted chemical and physical processes, render the application of methods of treatment based upon these conceptions a matter of great difficulty, and one which requires a high degree of conservatism in the interpretation of results. The union of toxin and antitoxin, which, as experiment has shown, follows the laws of other chemical reactions, is one of the simplest of the processes upon which methods of therapy are based, and yet in two diseases, diphtheria and tetanus, in many respects similar in that the damage to the body is caused by a soluble toxin which is produced in a local lesion, the effectiveness of the corresponding antiserum in the treatment of the disease is by no means the same. Diphtheria antitoxin has high curative value in diphtheria when used early in the disease; it is progressively less effective with each day of delay; it has also a definite protective value when used in those exposed to, but not yet ill with, the disease. Antitetanic serum has a high, though temporary, protective value when administered to persons who have suffered deep punctured wounds, compound fractures or lacerating wounds under conditions in which tetanus organisms may have been introduced; the effectiveness of antitetanic serum when used after symptoms of tetanus have appeared is much less, although in carefully controlled series it appears that the mortality is about 20 per cent less, in properly treated than in untreated cases. In diphtheria the attention of the physician is called early to the local lesion by which the diagnosis is at once made and treatment instituted; in tetanus the diagnostic symptoms appear only after extensive invasion of the nerve tracts has occurred, and treatment is inevitably delayed. Thus, in the two diseases, the effectiveness of specific antitoxic serum of proved potency is influenced by conditions peculiar to the diseases themselves, in this case the distribution of toxin relative to the time of appearance of symptoms.

When we pass to the interpretation of results of treatment by antisera in other diseases, or by bacterial products or vaccines, the problem is much more difficult than in those just mentioned in which the relatively simple chemical reaction of toxin and antitoxin is involved, and it soon becomes evident that, while our present knowledge of the chemical nature of immunity has served to point the way to possible means of specific therapy, the question as to whether these measures will be effective cannot be answered on theoretic grounds, but must await the results of practical application in each disease.

The greatest error involved in the estimation of the clinical effect of a remedy is the failure to take into full account the natural history of the disease in question. If we assume that in a given disease the outcome has heretofore been invariably fatal, and that, under a new method of treatment, even one or two recoveries have occurred in proved cases of the disease, this clinical evidence would be sufficient to establish the effectiveness of the remedy. In practice, however, in most of the infectious diseases, the clinical course, severity of symptoms, and outcome are variable, so that in order to judge of the value of the remedy, many observations are required which shall include equal numbers of treated and untreated cases, equally distributed throughout the period of observation. Even under apparently adequately controlled conditions, results which seem at first to indicate therapeutic value of a remedy are later shown to have been due to unrecognized factors which happened to combine to place the remedy in a favorable light unwarranted by the actual facts. To eliminate thoroughly the chances of error many series of cases treated by different observers are required to establish or disprove the claims of a method of specific therapy, which, judged on theoretic grounds alone, may have much to recommend it. And so in the past twenty-five years, of the many attempted methods of specific therapy, most of which have had some definite though perhaps limited basis in theory, a few have been proved to be of value and have become established as a part of clinical medicine; others have been discarded as ineffective or dangerous; others are still undergoing the necessary period of clinical trial required to determine their practical value. These various methods involve either the conferring of passive immunity by means of antisera from immunized animals or man, or the production of active immunity by the inoculation of antigens, usually preparations of bacteria or their products. Immune sera have also been combined with chemical preparations of known bactericidal powers, in attempts at chemoserologic therapy.

Active Immunization.—In addition to the immunity to certain diseases which follows recovery from them, active immunity may be acquired by inoculation of a modified form of the disease, as in vaccination against small-pox, or by inoculation of an attenuated virus, as in the prevention of rabies. One of the most striking examples of the successful application of active immunization in medicine is the prophylactic immunization against typhoid fever. The immunity here conferred is relative only, but it is usually sufficient to protect from infection under ordinary conditions of life. Some progress has been made by active immunization in the prevention of bubonic plague and cholera, and there is evidence to show that the incidence of pneumonia is somewhat less in large groups of persons who have been given protective inoculations of pneumococci than in untreated control groups. The protection so conferred has thus far not been sufficiently striking to warrant the general use of prophylactic vaccination against pneumonia. The use of toxin-antitoxin mixtures for immunization against diphtheria offers an apparently valuable method of prevention of the disease (see section on Diphtheria, Vol. II, page 482).

The achievements of active immunization by bacterial vaccines in the treatment of established infectious diseases are much more limited. In the treatment of localized infections such as furunculosis, active immunization by inoculations of staphylococcus vaccine has in the opinion of some careful observers been of value in stopping the succession of furuncles. Here, however, it seems probable that the treatment is in reality a prophylactic immunization against subsequent local infections.

In the treatment of generalized infections, the results obtained from inoculations of vaccines have not been such as to recommend the method. It is true that pronounced and at times startling effects, sometimes favorable and sometimes unfavorable to the patient, have followed the inoculations, but it appears that these effects are in part to be accounted for on the basis of non-specific protein shock which may be elicited by the inoculation of any foreign protein.

Foreign Protein Therapy (Protein Shock Therapy).—In addition to those methods which have been developed on the general principle of specificity in the reactions of the body to disease, some emphasis has recently been placed on certain apparently non-specific reactions of the body to disease. It has been noted that following the chill, fever and leukocytic changes which result from the intravenous injection of foreign protein, the fever, in diseases such as typhoid fever, may sometimes fall by crisis, or the local symptoms of pain and swelling in arthritis may disappear, and the attempt has been made to utilize this reaction in the treatment of infectious disease under the name of "protein therapy."

The intravenous injection of small quantities of foreign protein is followed within a few minutes to an hour or so by a rise in temperature, chill, sweating, and leukopenia followed by leukocytosis. Coincident and subsequent changes in serum protease and other ferments, and an increase in antibodies such as precipitins and agglutinins in previously immunized animals, occur. After the subsidence of the reaction in patients, there is frequently noted an improvement in the general condition, characterized by lowered fever, or decrease in the pain of affected joints in cases of arthritis. This improvement is often temporary; in some cases it is said to be permanent. This reaction can be elicited by many substances including proteoses, bacterial suspensions, such as typhoid vaccine, colloidal suspensions of metals, and hypertonic and hypotonic solutions of salt or sugar. It is thus clearly non-specific.[1]

Many theories have been advanced to explain the phenomena noted in the reaction. The appearance of specific antibodies such as agglutinins and precipitins in previously immunized animals seems best explained on the theory that the reaction causes a mobilization of antibodies previously formed, and it has been held that the favorable effects noted in some patients are due to this flushing out of specific substances. The secondary leukocytosis has also been urged as a factor favoring recovery. Those who do not hesitate to depart from the more exacting principles of specificity argue that we have heretofore been too much interested in the specific cause of inflammation, and in the methods of specific defense against it, and have neglected the more general and less specific reaction of the inflammatory process itself. As a problem for study, the reaction presents many phases, the investigation of which will undoubtedly throw light on the general question of the mechanism of recovery from disease.

We are here concerned, however, with the application of the method at present in the cure of infectious disease. Intravenous injections of foreign protein, or other substances designed to produce the phenomena of protein shock, have been used in many infectious diseases. In reviewing series of case reports in the various diseases in which favorable opinions of this method of therapy are expressed, one is at once struck with the lack of control cases. Then, too, there is often a total lack of consideration of the natural course of the disease under discussion, and sudden changes for the better are credited to the treatment, when a moment's thought would suggest a more simple explanation. Temporary improvement in joints following protein shock is frequently observed, and in some cases this improvement is continued; but often after the welcome improvement, relapse to the original condition occurs. For these reasons many of the favorable opinions must be heavily discounted. Judged from clinical reports, the case for protein shock therapy does not appear to be proved.

Admitting that in some cases improvement following protein shock has been prompt and lasting, it is in order to inquire whether these cases could have been selected previous to treatment, and, if not, how much danger is entailed in the routine treatment of all patients by this method.

As Petersen points out "if non-specific therapy is after all merely a method that deals with heretofore known reactions, we must be prepared to accept the probability that it obeys all the commonly observed laws of biologic reactions. If we regard it as a method of stimulation, plasma-activation, it follows that it can only be effective when the protoplasm is still in fit condition to respond to stimulation. Once the stage of exhaustion has been reached, the mere irritation of the non-specific agent is no longer able to bring about any alteration in the disease process, other than an aggravation."

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[1] Recently, injections of milk have been used for this purpose.—Editor.

Besides the possibility of decreasing resistance to disease, the danger of more serious results from intravenous injections of foreign protein must be considered. Deaths following protein shock are not usually reported, but it is well known that they occur. Even if deaths were less frequent than is the case, we should still pause to weigh the probability of improvement against the possibility, even remote, of fatal outcome.

There are certain emergencies, however, in which the possible dangers may be held to be less than the possible benefits to be derived from this method of therapy. It has been noted that following the production of protein shock, inflammatory processes in mucous membranes frequently subside. In gonorrheal ophthalmia, in which the patient is threatened with blindness if the inflammation is not quickly controlled, good results have been reported following the reaction produced by the intramuscular injection of milk. In severe and uncontrollable iridocyclitis, foreign protein injections have been credited with good effects. In such emergencies the trial of foreign proteins appears justified in selected cases. Further clinical study will determine the effectiveness of the method in this class of cases.

Care and conservatism are urged by those who have studied the effects of intravenous injections of proteins, but in their clinical use this conservatism appears sometimes to be more preached than practiced. At the present time, in the opinion of the writer, the routine use of intravenous injections of foreign proteins in infectious diseases is not justified by the results obtained. The balance of immunity is a very delicate one, which may be easily deflected for or against the patient, and we should not wish to alter this balance unless we can be reasonably sure that the change will be in favor of the patient.

CHAPTER III

NORMAL SERA AND BLOOD IN THE TREATMENT OF ANEMIA AND THE HEMORRHAGIC DISEASES

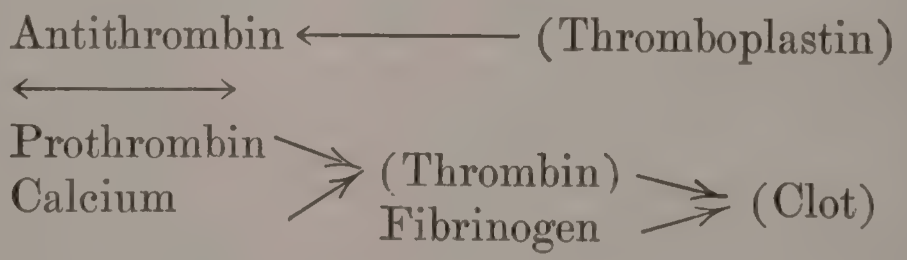
G. H. Whipple and W. L. Moss

MECHANISM OF COAGULATION OF THE BLOOD

G. H. Whipple

The group of hemorrhagic diseases is a very unsatisfactory and indefinite one. We may include here almost any disease with which purpura or bleeding is an important symptom. The tendency to hemorrhage is a symptom and not a true disease, and, like icterus, it is a symptom of a disease which affects some organ or tissue of the body. Some of the clinical entities are well recognized, and must be designated by their familiar names whether suitable, confusing, or otherwise.

The theories of blood coagulation are many and varied, and need not be reviewed. It is quite essential, however, to have clearly in mind the mechanism of normal blood coagulation. The theory of Howell meets the known requirements of blood coagulation in health and disease in the most satisfactory manner, and we may accept this as a working hypothesis until it is shown inadequate.



The substances included in parentheses are not present in the circulating blood. The prothrombin is held in an inactive state by the antithrombin which can be demonstrated in normal blood. Thromboplastin is freed by any tissue injury (blood-cells, plates, endothelium, etc.), and neutralizes the antithrombin, thus freeing the prothrombin. Coagulation then occurs by formation of thrombin and precipitation of the fibrinogen.

The logical method of classification and study of various types of hemorrhagic disease is to group them under the headings indicated in the schema given above for blood coagulation. This method has disadvantages, but also some advantages, as one is forced to look at a disease from a different viewpoint, which in itself may be helpful.

Fibrinogen.—This element fluctuates widely in amount in man and animals, but in health never falls to a dangerously low level (Whipple). Its rate of regeneration in health is extremely rapid (Goodpasture), and the reserve capacity of reproduction by the body seems limitless. This in itself indicates the great importance of the protein in the body economy. It may be greatly depleted by various poisons (chloroform, phosphorus) which injure the liver, and in severe poisoning the fibrinogen may practically disappear. This explains the disseminated ecchymoses, gastric hemorrhage, and bleeding noticed in such cases. The clots are too flabby to close any ruptured vessels. The hemorrhagic symptoms of acute yellow atrophy and yellow fever are referable to this drop in the blood fibrinogen to a very low level due to liver injury. Various chronic liver diseases (cirrhosis) may show a low fibrinogen index, and this is of very serious prognostic importance. This low fibrinogen index will favor hemorrhage. It is to be kept in mind, however, that liver disease may be associated with normal fibrinogen, but with abnormalities in other factors of coagulation.

From a theoretical standpoint there is no reason to expect any favorable reaction from serum treatment in such conditions. Whole blood might help to tide a patient over a period of acute fibrinogen insufficiency until regeneration of the liver cells can adjust the normal balance.

Calcium.—There is no evidence that any form of hemorrhage is referable to abnormality in this element. Icterus may show delayed coagulation time, which may be improved by calcium feeding, but in such cases the calcium blood content is above normal. It is probable that the calcium is bound by the bile pigments, and is only slowly available for the requirements of coagulation. There is no serious danger in this condition. True hemorrhagic symptoms with icterus may be associated with other abnormalities in blood coagulation (Whipple) and are considered below.

Prothrombin.—This elusive element is rarely involved in hemorrhagic disease. Hemorrhagic disease of the newborn in some, perhaps all, cases is associated with disappearance of this substance from the circulating blood (Whipple). There is good evidence that the prothrombin may be present at birth, but vanishes during the first few days of life. It is obvious that fresh serum which is rich in thrombin should be of value, and experience has confirmed this. Pure thrombin should be the ideal treatment. Hemophilia, according to recent work of Howell, shows a lowering of the prothrombin content of the blood plasma. Theoretically, then, one would expect help from serum injections.

Antithrombin.—The antithrombin-prothrombin balance is in very delicate equilibrium, and can be upset by various experimental procedures—for example, intravenous injection of peptone—but the capacity of the normal body to readjust this disturbed equilibrium is very great. It is pretty clear that the liver may be concerned with the production of antithrombin, and perhaps its destruction, but it is also certain that thrombin can in some way be neutralized in the blood outside of the liver. It is not surprising, then, that in disease one may meet with hemorrhagic symptoms, or periods which are due to excess of the antithrombin factor. This has been shown (Whipple) to be true in certain cases of septicemia, miliary tuberculosis, endocarditis, etc. It is possible that the rapid tissue destruction and disintegration may have freed substances capable of stimulating the liver to an overproduction of antithrombin. Another group of cases, leukemias and anemias, may show the same abnormality. This may be found in aplastic anemia with complete marrow aplasia, showing that the reaction of the bone marrow is not a factor in this complex.

Diseases of the liver with icterus may at times be associated with an antithrombin excess and develop grave hemorrhagic symptoms. It is obvious that calcium would be of no therapeutic value in cases of icterus with bleeding of this type. Cases of this type with mild icterus may develop for no apparent reason, and after a period in which bleeding may be troublesome and dangerous may suddenly return to normal without treatment of any kind. This fluctuation in the antithrombin content is quite obscure.

Other Factors.—It has been suggested that some types of hemorrhagic disease may be referable to increased fragility of the capillaries. This is simply an evasion of the point at issue, and no direct evidence has ever been adduced to support this view. Fewer and fewer cases will be grouped here as more definite data are accumulated to show the real cause of the bleeding.

Blood-platelets are known to fluctuate in disease, and it has been suggested by Duke that a great drop in the number of blood-plates may favor bleeding and purpura. It is possible that other elements of blood coagulation may fluctuate in a like fashion. Howell has reported cases of purpura in which no abnormality of blood coagulation was demonstrable, but the blood-plates were not counted.

Fibrin-dissolving ferments may be concerned in some cases of hemorrhage, even in fatal cases in adults. This ferment may be very active, and can dissolve blood-clots in vivo or in vitro with great rapidity. Consequently, even with normal elements of blood coagulation, the clots are not permanent, and oozing continues through the softened clots which form at the site of injury. This ferment may be present in small amounts (Goodpasture) in cases with liver disease, even if not sufficient to give rise to hemorrhagic symptoms. Normal blood plasma contains a ferment capable of inactivating this fibrinolytic ferment.

CLASSIFICATION AND TREATMENT OF THE ANEMIAS AND HEMORRHAGIC DISEASES

W. L. Moss

The blood is a fluid so essential to life that it is not strange that physicians in every age have sought to influence disease through this medium. The history of therapeutics from its earliest days abounds in the records of these attempts at blood therapy. The blood has been depleted by bleeding, cupping, leeching, purging, sweating; and efforts have been made to augment or otherwise alter it by the introduction of normal and abnormal blood from man and beast. Some of these methods are founded on a rational basis, and their proved value entitles them to a place in our present-day therapeutics; others are only of historical interest.

In recent years there has been such a revival of interest in the efforts to treat disease by means of the introduction of blood or its various constituents, and in some instances at least with such a measure of success that no treatise on therapeutics is complete without a discussion of the subject.

The use of the various immune or specific sera has been considered elsewhere in this volume, and the present chapter deals with the use of normal blood and its derivatives in the treatment of disease. The diseases to which this form of therapy has been applied consist mainly of the anemias and a large group of diseases in which hemorrhage may occur. From the latter group there may be separated a smaller group somewhat loosely designated as the hemorrhagic diseases.

A satisfactory classification of the anemias cannot be made, owing to our incomplete knowledge of their etiology. They are usually divided into primary, or essential, and secondary. "By primary is meant one for which an adequate cause cannot be assigned. By secondary anemia is meant one for which the cause assigned seems adequate to explain the blood condition" (Emerson).

Under primary anemias Osler mentions only two diseases: chlorosis and idiopathic or pernicious anemia. Many authors include here also the leukemias, Hodgkin's disease, and splenic anemia.

Some confusion has arisen from the use of the terms "primary type of anemia" and "secondary type of anemia." By the former is meant an anemia with a high color index, the latter is used to designate an anemia with a low color index. Thus chlorosis, which, on the basis of etiology, is classed as a primary anemia, is, on the ground of the color index, one of the best examples of the secondary type of anemia, and not infrequently carcinoma of the stomach leads to an anemia with a color index above one.

We have attempted to make etiology the basis of the following classification; it is, of course, tentative, and the primary group will diminish as the causes of the diseases included in it are discovered. If the observations of Negri and Miermet and Bunting and Yates on the bacterial nature of Hodgkin's disease had been confirmed, it would have placed this disease in the group of secondary anemias. The classification of the secondary anemias is taken from Osler.

ANEMIA

Primary or Essential Anemia

1. Chlorosis.
2. Idiopathic or Pernicious Anemia. Subtype—Aplastic Anemia.
3. Leukemia.
    - *a.* Myeloid or Splenomedullary.
    - *b.* Lymphoid or Lymphatic.
4. Splenic Anemia (Banti's Disease).
5. Pseudoleukemia (Hodgkin's Disease).

Secondary Anemia

1. Acute Secondary Anemia. Hemorrhage, certain acute infections, and intoxications are the important causes.

2. Chronic Secondary Anemia; of which the important causes are:

a. Inanition: due to defective food supply, unhygienic surroundings, chronic dyspepsia, cancer of esophagus and stomach.

b. Infections: especially typhoid fever, rheumatic fever, sepsis, syphilis, malaria, ankylostoma, and bothriocephalus.

c. Intoxications: inorganic poisons, such as lead, mercury, arsenic; organic poisons, such as the toxins of various fevers; and certain autogenous poisons occurring in chronic affections such as nephritis, jaundice.

d. Hemorrhage: repeated hemorrhages, even though small, such as the persistent bleeding from hemorrhoids.

e. Long-continued drains upon the system as in chronic suppuration, prolonged lactation, and rapidly growing tumors.

The difficulty in classifying the diseases with which hemorrhage may be associated is as formidable as that met with in the case of the anemias.

Under the designation Hemorrhagic Diseases we have separated a group whose striking and important characteristic is a tendency to im-moderate hemorrhage. The limits of this group are at present not very clearly drawn, but it should probably include only those diseases in which the tendency to bleed is dependent upon some disturbance of the factors concerned in the coagulation of the blood. If this is made the basis of the classification it will appear from the preceding discussion of the theories of coagulation that the group may be divided into subgroups, depending upon the particular factor or factors which may be at fault. Thus in one group might be included those diseases in which the hemorrhagic tendency depends upon a deficiency of prothrombin, another might include those in which there was an excess of antithrombin, a third might include those diseases in which the hemorrhage is due to deficient fibrinogen, and so on for each of the factors concerned in coagulation. Of course it is highly probable that the conditions are too complex to fit into any such simple classification as suggested above. It is probable that two or more factors may be disturbed simultaneously in some instances, and, moreover, it is even possible that in a given disease the same factors are not always at fault.

We have separated from the hemorrhagic diseases a large heterogeneous group which we have designated Diseases with which Hemorrhage may be associated. This group includes a number of infectious diseases due to bacteria, those due to animal parasites and those of unknown etiology. It also includes a variety of non-infectious diseases.

In some of the diseases of this group the anatomical lesions present seem adequate to explain the hemorrhage, and in such cases it is not necessary to presuppose the existence of any disturbance of the factors influencing coagulation. Thus in some instances the erosion due to ulcers in the stomach or intestines, the ulceration of neoplasms of the alimentary tract, genito-urinary system, and elsewhere, renal tuberculosis, or the presence of stone in the kidney or bladder may readily account for hemorrhage. But even in these easily explicable cases it seems likely that if the hemorrhage is sufficient to cause a marked grade of anemia which persists for a considerable length of time, there may be secondary changes in the blood leading to a disturbance in its coagulability which may prolong the hemorrhage. It seems not improbable, even in typhoid fever, a disease in which the intestinal hemorrhages are usually ascribed to the erosion of vessels by ulcers, that in many cases the important underlying cause of the hemorrhage is a disturbance of the balance between the factors upon which coagulation depends. The same may be true of the hemorrhage in certain cases of tuberculosis.

In other diseases included in this group, septicemia, diphtheria, variola, scarlet fever, measles, typhus fever, yellow fever, scurvy, and acute yellow atrophy, the hemorrhagic tendency is not so easily explained, and is rather vaguely considered to be toxic in origin.

The desirability of a knowledge of etiology for the classification of the hemorrhagic diseases has already been pointed out; it is even more desirable for the treatment.

There have been no studies, so far as we know, in which all of the factors influencing coagulation have been investigated simultaneously. A number of observers have followed one or several of the factors, and such data as are available indicate that a disturbance in certain factors may be characteristic for a given disease, but the observations have been so incomplete, and the series of cases so small, that generalizations would be unsafe.

Rather than attempt a classification on an etiological basis, which would not only be incomplete, but almost certainly faulty, it seems wiser to refer very briefly to the findings in the few cases which have been at all carefully investigated, and trust that the recognition of the sort of studies that are necessary to advance our knowledge on this important subject will stimulate investigators to further work in this field.

HEMORRHAGIC DISEASES

1. Hemophilia.
2. Morbus Maculosus Neonatorum.
3. Purpura.
   - *a.* Purpura Simplex.
   - *b.* Purpura Rheumatica.
   - *c.* Purpura Hæmorrhagica.
4. Essential Hematuria.

Diseases with Which Hemorrhage May Be Associated

Typhoid Fever.
Septicemia.
Diphtheria.
Pertussis.
Dysentery, bacillary and amebic.
Plague.
Tuberculosis.
Malaria.
Relapsing Fever.
Syphilis.
Pulmonary Distomiasis.
Bilharziosis.
Filariasis.
Variola.
Varicella.
Scarlet Fever.
Measles.
Typhus Fever.
Yellow Fever.
Dengue.
Rocky Mountain Spotted Fever.
Plumbism.
Pellagra.
Scurvy.
Cirrhosis Ventriculi.
Gastric and Duodenal Ulcer.
Ulcerative Enteritis and Colitis.
Cancer of Alimentary Tract and Genito-urinary System.
Diseases Associated with Jaundice.
Hepatic Cirrhosis.
Nephritis.

Diseases with Which Hemorrhage May Be Associated.—*Cont.*

- Pernicious Anemia.
- Leukemia.
- Splenic Anemia.
- Epistaxis Due to Local Causes.
- Genito-urinary Conditions Due to Stone, Neoplasms, and Infections.
- Diseases of the Female Generative Tract.

METHODS OF TREATMENT

Since we are going to consider relatively few agents which may be applied in the treatment of a great variety of conditions, it will save much repetition to describe the agents employed, their source, preparation, properties, mode of action as far as known, and methods of administration, before discussing their prophylactic and therapeutic application. The agents are: (1) normal serum (in contradistinction to immune); (2) defibrinated blood; (3) citrated blood; and (4) whole blood. Either human or animal serum may be employed, but when defibrinated blood or whole blood is used it should be of human origin.

In the use of human blood or serum care should be exercised that the donor is a strong, healthy individual, or at least one free from communicable disease. Syphilis especially should be excluded, not only by a negative history, but by a negative Wassermann reaction.

Serum

A variety of sera have been employed; for instance, horse, sheep, goat, beef, rabbit. Beef and goat sera are said to be more toxic than the others, and on that account their use is less desirable. Although normal horse serum may be obtained from a number of the large drug houses which manufacture antitoxins, it would be difficult to get it as promptly as might be necessary, or as fresh as it seems desirable to use it. Another objection to its use is the possible danger from anaphylaxis in a patient who has previously received antitoxin (horse serum), or of sensitization in one who might subsequently develop the need for antitoxin. Although the danger from anaphylaxis has probably been greatly exaggerated, it seems wiser to avoid the risk when possible. Good results in the treatment of hemorrhage have been reported from the use of antitoxic serum, but it is doubtful if this agent is as useful as fresh serum.

The rabbit furnishes the most convenient source of fresh supply, and its serum is not only without toxicity in the doses employed, but appears to be the most efficacious of the animal sera in the treatment of hemorrhage.

To Obtain Rabbit Serum.—A large, healthy rabbit is selected, anesthetized, the front of the thorax is shaved and the skin rendered aseptic. Blood is aspirated from the heart through a needle of fairly large caliber by means of a sterile 20 c.c. syringe. The needle is inserted at a point about 1 cm. to the left of the midline and 1 cm. above the level of the costal angle, being directed upward and toward the midline. Usually as much as 60 c.c. of blood may be obtained from a good-sized rabbit without sacrificing the animal. If more than 20 c.c. of blood is desired it is convenient to use a needle which is attached to the syringe by means of a push connection rather than a screw connection. After the syringe has been filled it is detached from the needle, which remains in situ, and the blood is transferred to a sterile centrifuge tube. A second, and even a third, aspiration of blood may usually be made with the same syringe if one works rapidly, but it is well to have a second syringe ready in case the blood begins to coagulate in the first. As soon as the blood is coagulated the clot is detached from the sides of the centrifuge tubes by means of a sterile platinum needle, and the serum is allowed to separate. After one to two hours the tubes may be centrifugalized and the serum removed by means of a sterile pipette. If the serum is intended for intravenous injection it should be entirely free from cells. These may be removed, if present, by further centrifugalization. If it is to be injected subcutaneously the admixture of a few cells does no harm.

To Obtain Human Serum.—If only a small quantity is desired the blood may be aspirated from one of the large veins at the bend of the elbow by means of a syringe. In case a larger quantity is desired than can be obtained conveniently with a syringe one may employ an aspirating outfit made in the following way: A 100, 200, or even 250 c.c. glass cylinder is fitted with a rubber stopper, through which are passed two glass tubes about three inches long, bent at the middle to a right angle. To the outer end of one of these tubes is attached a short needle of fairly large caliber by means of a rubber tube one or two inches long. To the other glass tube a small vacuum pump is attached by means of ten or twelve inches of thick-walled rubber tubing. The attachment of glass tubing equipped with pledgets of cotton to prevent access of bacteria is not necessary when the pump is used. This apparatus is sterilized by boiling. A bandage is placed around the upper arm of the person from whom the blood is to be obtained, sufficiently tight to cause the veins to stand out prominently, but not tight enough to obliterate the radial pulse. The skin having been previously cleaned, the needle of the aspirating apparatus is inserted into a vein and the flow of blood into the cylinder accelerated by suction applied through the opposite tube. After the desired amount of blood has been obtained the bandage is removed from the arm, the needle withdrawn from the vein, and a sterile sponge quickly placed over the puncture wound, and moderately firm pressure applied for a half minute to a minute to prevent the possible formation of a hematoma.

The rubber stopper in the cylinder is replaced by a sterile cotton plug, and as soon as the blood has coagulated the clot is separated from the sides of the cylinder by means of a small sterile glass rod. The serum is allowed to separate, and after several hours is removed by means of a sterile pipette and rubber bulb.

Properties of Serum.—Normal serum differs from whole blood in that it contains no cellular elements, although it may contain substances (thromboplastin?) liberated by the disintegration of platelets and leukocytes. It contains no fibrinogen, no antithrombin, and less calcium salts than the blood. It contains no prothrombin, but free fibrin ferment (thrombin), which is not present in whole blood. Morawitz and others have shown that on standing a few days thrombin is converted into an inactive form, metathrombin. This may explain the better results following the use of fresh serum.

Action of Serum.—Clinical results have proved that serum, administered subcutaneously or intravenously, is a valuable hemostatic in some cases of hemorrhage. Also that it may be a valuable prophylactic agent before operation in individuals with a hemorrhagic tendency, but we are as yet ignorant of its mode of action. It has been used fairly extensively, and the accumulated experience indicates that there is little, if any, danger of producing intravascular clotting.

Howell has shown that large amounts of serum, and even of pure thrombin, may be injected intravenously in animals without apparent injurious effects. The antithrombin content of the blood may show an increase a few hours after such injections, but quickly returns to normal. This increase in antithrombin might be regarded as a contra-indication to the use of serum in cases where the hemorrhagic tendency depends upon an excess of antithrombin, and the same might apply to the use of defibrinated blood. It should be taken into consideration, however, that these observations were made upon animals whose blood was presumably normal as regards the factors influencing coagulation, and it is not certain that they would apply to human beings whose hemorrhagic tendencies lead us to presuppose some disturbance of these factors. While emphasizing the value of such observations, and the importance of any study that will throw light on the mode of action of these agents, we feel that the question of their usefulness will be determined on a basis of clinical results.

Animal and human serum appear to be equally efficient in the treatment of hemorrhage.

Methods of Administration.—Serum may be given subcutaneously in doses of 10 to 30 c.c., or intravenously in doses of 10 to 15 c.c. It is apparently more prompt in its action and more efficacious if given intravenously. Sometimes a single dose suffices to stop the hemorrhage. In case of continued bleeding the dose may be repeated at intervals of two to six hours, or even longer, depending upon the urgency of the indications. If the bleeding is not controlled by the first few administrations of serum little good can be expected from its continued use. There is no danger from anaphylaxis attending the use of human serum. In case animal serum is used it is advisable to ascertain whether the patient has ever received a previous injection of serum from the animal species to be used. The danger from anaphylaxis attending intravenous injection is greater than that from its subcutaneous use. There is no danger from anaphylaxis when the last injection is made within seven days of the first injection. If necessity should arise for further serum treatment after a lapse of more than seven days from the first serum injection it would be wise to use serum from an animal of a different species.

DEFIBRINATED BLOOD

Defibrinated blood may be given subcutaneously in small amounts, or intravenously in amounts up to 600 c.c. It differs from whole blood in that the platelets and, to some extent, the leukocytes have been destroyed, but, as in the case of serum, it may contain some of the disintegration products (thromboplastin?) of these cells. It has been deprived of its fibrinogen and antithrombin, and the amount of calcium salts has been reduced. The prothrombin has disappeared, and it contains free fibrin ferment.

Mode of Action.—Defibrinated blood in small amounts subcutaneously or intravenously would appear, a priori, to have the same action as serum similarly introduced, except for any additional action which may be due to the presence of the red blood-cells. A discussion of this subject will be deferred until we come to consider the treatment of pernicious anemia. Large amounts of defibrinated blood have been employed intravenously in place of direct transfusion in a variety of conditions. Experimental results indicate that the red blood-cells introduced are able to live and functionate in the patient's circulation. The presence of the large amount of thrombin is apparently well tolerated. The observation previously mentioned, namely, that the introduction of thrombin stimulates the body to the production of an excess of antithrombin, might be considered a contra-indication to the use of this method in patients where the hemorrhagic tendency is dependent upon an excess of antithrombin, and the method may prove useless in those cases where the faulty coagulation depends upon an absence or deficiency of fibrinogen. Apart from these theoretical objections, the value of the procedure will probably ultimately be determined by the clinical results.

It should be noted that the introduction of defibrinated blood is frequently followed by a febrile reaction on the part of the patient. This usually begins within an hour, and may be accompanied by a chill. The temperature may reach 103° F., or higher, but falls to normal in a few hours. This reaction does not seem to detract in any way from the value of the procedure.

Preparation of Defibrinated Blood.—To obtain small amounts blood is aspirated from an arm vein of the donor by means of a syringe, and transferred to a sterile flask containing glass beads, and shaken for ten minutes. If it is for intravenous administration it should be filtered through several layers of sterile gauze after defibrination. This precaution may be omitted in case of subcutaneous injection.

Intravenous Administration of Large Amounts of Defibrinated Blood.—One of us has described a simple technic for indirect transfusion, the details of which may be found on reference to the original article. Briefly, the procedure may be described as follows: The apparatus for obtaining and defibrinating the blood consists of several Erlenmeyer flasks of 300 c.c. capacity, each containing about one ounce of glass beads and stoppered with cotton, a rubber stopper through which are passed two short glass tubes, to one of which is attached a short needle of moderately large caliber, to the other six or eight inches of thick-walled rubber tubing, to which a small vacuum pump is attached.

The flasks are sterilized by dry heat, the rest of the apparatus by boiling. Previous to use the inside of the needle and attached tube of the aspirating outfit are coated with sterile paraffin. The stopper carrying the needle is then fitted to one of the flasks containing glass beads, and the blood is aspirated from an elbow vein of the donor. When about 200 c.c. of blood has been obtained the flask is removed from the stopper without disturbing the needle in the vein, another flask is substituted in its place, and more blood aspirated. The above procedure is repeated until the necessary amount of blood is obtained. As soon as each flask is filled it is stoppered with a plain rubber stopper and shaken for ten minutes to defibrinate the blood. For an adult the optimum amount of defibrinated blood appears to be about 500 c.c. This amount is readily obtained from 600 c.c. of whole blood. The defibrinated blood is next filtered into an infusion bottle through several layers of sterile gauze and it is then allowed to flow by gravity into a vein of the patient.

Citrated Blood

The use of defibrinated blood has been largely superseded by the employment of citrated blood. The method of obtaining and administering the citrated blood is the same as that for defibrinated blood with the exception that sodium citrate is substituted in the collecting flask for the glass beads; 10 c.c. of a two and one-half per cent solution of sodium citrate in distilled water being used for every 100 c.c. of blood to be withdrawn.

The rate of administration should be 100 c.c. of citrated blood in four to six minutes, the rate being regulated by means of a thumb screw clamp on the delivery tube.

WHOLE BLOOD

Intravenous Use of Whole Blood.—With the recognized importance of transfusion we may confidently expect the development of a satisfactory technic for indirect transfusion of whole blood. Linderman has recently published a method which consists in introducing a specially designed cannula into a vein of the donor and a similar cannula into a vein of the patient. By means of a large number of 20 c.c. syringes blood is withdrawn from the donor and injected into the patient, a fresh syringe being used for each transfer of blood.

Kimpton and Brown proposed a method for indirect transfusion of whole blood. The apparatus consists of a glass cylinder of 200 or 300 c.c. capacity, the lower end of which is drawn out into a small tube bent at right angles to the axis of the cylinder. The inside of the cylinder and tube is coated with paraffin to prevent coagulation. The end of the tube is introduced into an arm vein of the donor and blood allowed to flow into the cylinder under the heightened venous pressure produced by a bandage around the upper arm. The tube is then removed from the donor's vein and introduced into a vein of the patient. The introduction of the blood into the patient is brought about by pumping air into the upper end of the cylinder. Exercise great care that no air is introduced into the patient's vein.

In the case of direct or indirect transfusion of either whole blood or defibrinated blood it is important, where possible, to select a donor who belongs to the same iso-agglutinin group as the donee. Methods for making this determination have been described elsewhere. The test may be carried out in the absence of known groups as follows: A few drops of blood are collected from the ear or finger tip of the patient in a glass tube, as for the Widal reaction, and allowed to coagulate in order to furnish serum. An additional drop or two of blood is allowed to fall into a centrifuge tube containing a few cubic centimeters of 1.5 per cent sodium citrate solution in 0.85 per cent sodium chlorid solution. The corpuscles thus obtained are washed twice in normal salt solution and then brought to approximately a 1 per cent suspension in normal salt solution. In a similar way serum and corpuscles are obtained from the prospective donors. The agglutinating action of the serum of the patient is tested against the corpuscles of each of the prospective donors, and the serum of each of the donors is tested for its agglutinating action against the corpuscles of the patient. This test may be made in the hanging drop by adding a small drop of the serum to an equal quantity of the suspension of corpuscles. The presence or absence of agglutination may be observed under the microscope. If the serum of individual A does not agglutinate the corpuscles of individual B, and if B's serum does not agglutinate A's corpuscles, the two individuals belong to the same iso-agglutinin group. It is not necessary to test for isohemolysins, since it has been shown that isohemolysins, when present, follow the same laws which govern iso-agglutination.

APPLICATION OF METHODS OF TREATMENT

Primary Idiopathic Anemia

Chlorosis.—Rarely the degree of anemia in this condition may reach an extreme grade, but the response to general hygienic measures and the administration of iron are so satisfactory that the necessity of resorting to any of the methods of treatment considered in this chapter would scarcely arise.

Pernicious Anemia.—The frequency with which this condition resists the usual therapeutic measures has ever led clinicians to try new measures with the hope of obtaining more satisfactory results. The usual type of pernicious anemia is characterized by remissions, during which there is improvement, followed sooner or later by relapse, and eventually a fatal termination. There is hyperplasia of the bone marrow in this type of the disease and evidence of an attempt at regeneration of the blood. Hemorrhages from the skin and serous surfaces are common. The coagulation and bleeding time are often prolonged. The blood-platelets are usually decreased in number, rarely increased. In the treatment of pernicious anemia the first essential is a correct diagnosis. Intestinal parasites which might account for the anemia should be excluded, and the existence of malignant neoplasms, especially carcinoma of the stomach, should be carefully investigated. The frequent occurrence of gastric anacidity in pernicious anemia is a point to be borne in mind, and is best treated by the administration of full doses of hydrochloric acid. The importance of discovering and removing any focus of infection, especially buccal and gastro-intestinal infections, has been emphasized by William Hunter.

The subgroup, aplastic anemia, differs from the usual type of pernicious anemia in that the bone marrow is aplastic, the cases run a rapid and progressive course without remissions, hemorrhages are more common and may be very severe. The coagulation time and bleeding time are increased. Whipple investigated a case in which he found the delay in coagulation time associated with an excess of antithrombin, the other factors concerned in coagulation being normal. Duke found great reduction in the number of platelets in his cases.

The methods of treatment considered in this chapter may be directed against the anemia itself or only against the hemorrhage. We will consider first treatment directed against the anemia without reference to hemorrhage. Small injections (10 to 20 c.c.) of defibrinated blood given subcutaneously or intravenously, and repeated at intervals of a few days, have been reported by Morawitz and others. Improvement is said to follow this procedure, the supposed effect being stimulation of the bone marrow. If this treatment is adopted it may be desirable from theoretical considerations to use blood from a member of a different iso-agglutinin group from that of the patient, with the hope that it may prove a more efficient stimulus to the bone marrow than the introduction of corpuscles homologous to those already in the circulation. It even seems doubtful if further stimulation of the bone marrow is desirable, since the mere presence of anemia forms a powerful stimulus for the hemopoietic organs. This is indicated by the regeneration forms present in the blood in the usual type of pernicious anemia. In the aplastic type we may well imagine that the stimulus is present, but that the bone marrow is no longer capable of response, perhaps as a result of exhaustion following overstimulation, and the protection of the hemopoietic organs from this excessive stimulation seems a more rational form of treatment. With this end in view one may attempt to relieve the anemia at once by transfusion. Direct transfusion may be employed, but, for the reasons given above, the indirect transfusion of whole blood, with or without citration, seems preferable. During the past three years we have employed the indirect transfusion of defibrinated blood in a number of cases of pernicious anemia with very encouraging results. The treatment consists in the introduction of 500 c.c. amounts of defibrinated blood at intervals of one to two weeks, thereby relieving the anemia rather rapidly. Two, three, or four such injections may be necessary. The interval between injections is determined by the blood count. The introduction of 500 c.c. of blood usually increases the count by about 500,000 red cells. Following the first, and sometimes the second, transfusion the count may gradually fall. Counts should be made every second or third day, and the next injection be given before the original level is reached. It is difficult to give precise indications, but the next injection might be given at a time when the count is still 200,000 cells in excess of the number preceding the last injection. Following the third or fourth transfusion, in favorable cases the count does not decline, but may show a progressive increase.

Treatment of the Hemorrhage in Pernicious Anemia.—The hemorrhagic tendency, as well as the anemia, may be successfully combated by the transfusion of large amounts of blood by one of the methods just described, but in case other measures are employed for the treatment of the anemia the hemorrhagic tendency may be treated by injections of normal rabbit or human serum in doses of 15 c.c. intravenously or 30 c.c.

subcutaneously, repeating the injections at intervals of twenty-four hours until three or four injections have been given.

Leukemia.—This group of diseases is characterized by a great increase in the leukocytes of the blood with hyperplasia of the leukoblastic tissues. With the progress of the disease a well-marked anemia usually develops which may become of extreme grade. Hemorrhages are not infrequent. The bleeding may be from the skin, mucous or serous membranes. Hemorrhagic retinitis may occur, and profuse epistaxis may lead to a rapidly developing anemia. The blood-platelets are usually increased. This is especially true of the myeloid form. The coagulation time in some cases is delayed. Whipple investigated a case of myeloid leukemia with purpura and profuse epistaxis in which the blood showed an increase of antithrombin. For the treatment of hemorrhage in leukemia one may resort to the injection of serum, as previously described, and if the anemia reaches a dangerous grade one may transfuse. It should be remembered that this treatment is symptomatic, and probably has no direct influence on the leukemic condition which should be treated by appropriate measures.

Splenic Anemia.—This disease is usually associated with a marked anemia of the secondary type which may reach an extreme degree. Hemorrhages are common, and may occur in the skin or from the mucous surfaces. Hematemesis has brought about a fatal issue in a number of cases.[1] For the milder grades of hemorrhage injections of serum may be employed. In the cases with a grave anemia transfusion may temporarily relieve the anemia. The only curative measure known is splenectomy. The mortality from this operation is high, owing perhaps to the fact that many of the patients are suffering from a severe grade of anemia, and to the further fact that the operation is attended with grave danger of hemorrhage from the enlarged vasa brevia which are frequently present in this disease. If the patient is anemic at the time he presents himself for operation a preliminary transfusion may do much toward lessening the risk of the operation, and in a number of instances simultaneous transfusion has been employed at the time of operation.

SECONDARY ANEMIA

We need consider here only the secondary anemia following hemorrhage. A discussion of the anemia associated with acute infections, intoxication, and other conditions will be considered when we come to discuss the diseases with which hemorrhage may be associated.

Acute Anemia Following Hemorrhage.—If the hemorrhage has not been excessive, and has stopped spontaneously, or has been controlled by direct means (compression, ligation, suture, etc.), little need be done beyond the ordinary upbuilding measures: rest, suitable diet, and the administration of iron. If the hemorrhage has been so severe as to endanger life the first indication is to stanch the flow of blood, if the bleeding point be accessible, and follow this immediately by a blood transfusion. If the hemorrhage cannot be checked by direct measures one may still resort to transfusion with the hope that a spontaneous cessation of the hemorrhage may take place and that the blood introduced may serve in the meantime to prevent dangerous depletion. In such cases care should be taken not to introduce enough blood to raise the pressure to a degree which would tend to cause a continuation of the hemorrhage. It is desirable to introduce just enough blood to prevent the total amount in the body from falling to a dangerously low level. Indirect transfusion in such cases appears to be the method of choice, as it enables the operator to control exactly the amount of blood introduced.

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[1] These are probably cases of thrombophlebitic splenomegaly and not true splenic anemia. The treatment is, however, the same (see chapter on Diseases of the Spleen, Vol. IV).—EDITOR.

Chronic Secondary Anemia.—Usually the primary indication in the treatment of the chronic secondary anemias following repeated hemorrhages is to remove the cause of the bleeding, for example, excision of gastric or duodenal ulcer, cauterization or packing in case of epistaxis, curettage for metrorrhagia, removal of hemorrhoids, or by such other measures as are appropriate. If the anemia is of an extreme grade transfusion may furnish the only hope of bringing operative procedures to a successful issue. Little good can be expected from injections of serum in such case unless the hemorrhage depends, in part at least, on a disturbance in the coagulability of the blood which may be favorably influenced by serum injections.

The chronic secondary anemia following repeated hemorrhages may reach an extreme grade even when the individual hemorrhages are small. We have recently seen two cases in which the hemoglobin was reduced to 10 per cent. One followed bleeding hemorrhoids, and the other persistent metrorrhagia. Following a transfusion of 550 c.c. defibrinated blood in the first case the hemoglobin rose to 35 per cent, where it remained about stationary for three to four weeks, further gain apparently being balanced by the continued bleeding from the hemorrhoids. A second injection of defibrinated blood raised the hemoglobin to 55 per cent, and the patient was transferred to the surgeons for operation.

The case of metrorrhagia illustrates the value of transfusion in connection with operations in the presence of a severe anemia. This patient entered the hospital on January 23, 1914, with a red count of 1,080,000 and hemoglobin of 10 per cent. Operation was decided upon, and as a preliminary measure 600 c.c. defibrinated blood was given, which raised the red count to 1,980,000 cells and the hemoglobin to 25 per cent. On the following day hysterectomy was performed by Dr. J. C. Neel, a second injection of defibrinated blood, 500 c.c., being given during the operation.

The following day the blood examination showed 2,688,000 red cells and hemoglobin 40 per cent. The patient left the hospital three weeks later with 3,256,000 red cells and hemoglobin 45 per cent.

THE HEMORRHAGIC DISEASES

Hemophilia.—Hemophilia furnishes the example *par excellence* of a hemorrhagic disease. This condition has been the object of extensive study by numerous investigators, the results of which have been so at variance that it seems unnecessary to discuss them here. Howell, in his recent investigations, concludes that "the blood in this condition is deficient in prothrombin. The antithrombin may be normal or somewhat greater than normal. The characteristic peculiarity of hemophilic blood is its markedly delayed time of coagulation. This peculiarity is explained by the diminution in amount of the prothrombin which results in a relative excess of antithrombin."

Weil and others have reported favorable results in the treatment of hemorrhage in this condition from the intravenous injection of fresh serum. This procedure may be useful as a prophylactic measure before minor operations which may be necessary in these patients, such as extraction of teeth, etc.

For the treatment of severe anemia following prolonged bleeding in this disease transfusion should be employed. Direct transfusion is contraindicated owing to the danger of uncontrollable hemorrhage even from the slight incision necessary in carrying out the procedure. This danger is not present when the blood is introduced by means of a needle inserted through the skin into a vein of the patient, as the elasticity of the vessel wall closes the needle puncture wound.

Morbus Maculosus Neonatorum.—Under the heading Hemorrhagic Diseases of the Newborn are grouped a variety of conditions which unfortunately some authors have not been careful in distinguishing from each other. Holt, under the title "The Hemorrhagic Disease of the Newly Born," separates a disease characterized by multiple hemorrhages of unknown etiology and not associated with syphilis or sepsis. The bleeding may come from the stomach, intestines, mouth, nose, umbilicus, conjunctivæ, ears, and the skin. The condition comes on usually during the first week of life, is of brief duration and high mortality, and is self-limited. It is not a manifestation of hemophilia, and the term hemophilia neonatorum should not be applied to it. Osler draws attention to the fact that not every case of melena neonatorum belongs in this category, as ulcer of the esophagus, stomach, and duodenum may give rise to the presence of blood in the stools and, in some instances, the blood which appears in the stools may even be drawn from the breast of the mother.

In the study of this group of cases great care should be exercised to determine the exact nature of the condition present and to designate it by a name which will not lead to confusion. Instead of designating one disease by a name which is descriptive of the whole group, it would perhaps be better to employ the less usual, and not adequately descriptive, but more individual name, morbus maculosus neonatorum. We have but little data upon which to draw conclusions as to the underlying cause of the hemorrhagic tendency in this condition.

Whipple investigated two cases which seem to fall in the above category, and although in one the mother gave a positive Wassermann reaction, the placenta was normal and no evidence of syphilis was found at the autopsy of the infant. The blood of both cases showed a markedly delayed coagulation time, and there was complete absence of prothrombin.

The results of the treatment of this disease by transfusion and by serum injections have been most gratifying. Cures have been reported in a large number of cases. If the amount of blood lost has been large, and the resulting condition of the infant is critical, immediate transfusion of blood is indicated. The amount of blood introduced should probably not exceed 200 c.c. If the hemorrhage has not led to a severe anemia, and the condition of the child is fairly good, satisfactory results may usually be obtained by the intravenous injection of fresh rabbit or human serum in 10 c.c. doses or the subcutaneous injection of 15 to 20 c.c. amounts. The disease is of short duration and self-limited, progressing to death or recovery in a few days. The mortality in 709 cases collected by Townsend was 79 per cent. Prompt and vigorous treatment is demanded. The serum injections should be repeated at intervals of three to six hours, and if the bleeding continues transfusion should be resorted to before the patient's condition becomes too serious. Schloss and Commiskey have reported good results from the subcutaneous injection of whole blood in 10 c.c. amounts. In a case which recently came under our observation the bleeding was apparently uninfluenced by this procedure, and twelve hours later there was no evidence that the blood injected had been absorbed. Two subcutaneous injections of pure thrombin prepared according to Howell's method were then given by Dr. Goodpasture. The hemorrhage ceased after the second injection and the patient left the hospital a week or ten days later in satisfactory condition.

Arthritic Purpura.—Under this heading two types of purpura are described, purpura simplex and purpura rheumatica. We have never seen any good results attend the use of serum injections in these conditions, although there are a number of favorable reports in the literature. The method seems worthy of a further trial in these cases.

Purpura Hæmorrhagica.—In addition to purpura there may be excessive hemorrhages from the mucous membranes, epistaxis, hematemesis, and hemoptysis, leading to a profound anemia and, in some instances, a fatal termination. Duke has reported a great reduction in the number of platelets in the cases studied by him. Howell found no disturbance of the prothrombin-antithrombin balance in his cases, but the number of cases studied is too small for generalization. There are many reports of prompt and completely successful results from the use of fresh human serum and normal rabbit serum in the treatment of these cases. If this measure fails, and the hemorrhage has reached alarming proportions, transfusion should be performed.

Essential Hematuria.—The etiology of this condition is entirely unknown, and we have been unable to find any data upon the condition of the blood in this disease. Injections of normal serum may be tried, and if the anemia has reached a dangerous degree transfusion may be employed.

Diseases with Which Hemorrhage May Be Associated

It would be useless to go through the long list of diseases given under this heading and attempt to point out the conditions in which the methods of treatment considered in this chapter might be applicable. In a majority of cases the necessity for the introduction of serum or blood would not arise, and in those cases where it did arise one should attempt to meet the indications of the individual case. In the following pages only a few of the diseases mentioned will be discussed.

Typhoid Fever.—In this disease the coagulation time of the blood may be shorter or longer than normal, corresponding perhaps to the occurrence of thrombosis in some cases and to hemorrhage in others. There can be little doubt, we think, that the bleeding in many cases of typhoid fever is accompanied by a disturbance in the balance of the factors influencing coagulation. We have treated a number of cases of typhoid hemorrhage by intravenous injection of serum, and while realizing the difficulty of drawing conclusions from anything less than an extensive series of cases, we feel that the results warrant a further trial of the method. In cases where the hemorrhage has been profound we have not hesitated to resort to the indirect transfusion of blood in 500 c.c. amounts.

Tuberculosis.—In the chronic pulmonary form of the disease the hemorrhage is most frequently due to the erosion of vessels or the rupture of small aneurisms in the lungs. It seems unlikely that the bleeding in such cases would be influenced by any of the measures under consideration here. Cases of tuberculosis occur, however, in which there appears to be a disturbance of the coagulability of the blood. Duke reports a case of tuberculosis associated with purpura which showed a prolonged bleeding time and low platelet count. He also reported a case of tuberculosis associated with epistaxis in which the bleeding time was prolonged and the platelets reduced. Whipple reports a case of miliary tuberculosis with profuse epistaxis in which the examination of the blood showed a low fibrinogen content.

Pellagra.—Transfusion has been recommended for the treatment of this disease. The series of cases thus far reported are too few to permit of drawing conclusions. Moreover, the dietetic treatment of this condition as recommended by Goldberger has proved so satisfactory that no necessity should arise for transfusion.

Gastric and Duodenal Ulcers.—The hemorrhage in this condition is dependent upon the erosion of vessels by the ulcer, and in the acute cases there is probably no disturbance in the coagulability of the blood. If the bleeding has been copious, resulting in the production of an acute anemia, the transfusion of whole or defibrinated blood is indicated. The blood-pressure should be observed during the operation, and the amount of blood introduced should not be large enough to increase the pressure above normal.

A recent experience may be reported in this connection. The patient, a very robust iron worker, without any previous symptoms pointing to gastric ulcer, suffered three profuse hematemeses on the night of March 3, 1914. Following the third hematemesis he fell unconscious to the floor. The next day he was brought to the hospital in a weakened condition, and on admission the blood examination showed:

R. B. C.	4,228,000
W. B. C.	21,800
Hb.	66 per cent

The patient continued to vomit copious amounts of blood on March 4 and 5, and the feces contained much dark blood. The blood count on the evening of the latter day had reached the following figures:

R. B. C.	2,080,000
W. B. C.	15,600
Hb.	30 per cent

The blood-pressure ranged between 60 and 80 mm. of mercury. At this time 18 c.c. of fresh rabbit serum was given intravenously. Following this injection there was but one hematemesis. This occurred the next day, and while the amount was only 50 c.c. it was followed by a syncopal attack, and tarry stools continued to be passed. On March 6 the red cells were 1,672,000 and the hemoglobin 25 per cent, and later in the day fell to 22 per cent. The respirations were sighing in character, and the patient semicomatose. The condition seemed so critical that it was decided to transfuse. A donor was selected of the same iso-agglutinin group as the patient, and 230 c.c. defibrinated blood was introduced. The blood-pressure was observed at intervals of a few minutes during the procedure, and the transfusion discontinued when the pressure reached 118 mm. of mercury, as it was feared that a further increase of pressure might start the hemorrhage again. After six or eight hours the pressure had fallen to 80, and a second injection, 475 c.c. defibrinated blood, was given. This was followed by a striking improvement in the patient's condition. The blood count showed on March 7, R. B. C. 3,116,000, Hb. 40 per cent, and on March 10, R. B. C. 3,200,000, Hb. 44 per cent, since which time the convalescence has progressed satisfactorily. Although the diagnosis in this case remains in some doubt, the indication for transfusion seemed clear enough, and the results may, with reasonable confidence, be referred to this measure.

Jaundice.—Although the hemorrhagic tendency in many cases of jaundice has long been recognized, no satisfactory explanation has been brought forward to account for it. Whipple and King have suggested that the bile pigments have combined with the calcium salts of the blood in such a way as to render them incapable of playing their part in the formation of thrombin.

Morawitz and Bierich maintain that, although the bile and the gallic acid salts are capable of inhibiting coagulation, the concentration necessary for this action is never reached in the circulating blood. The coagulation and bleeding time may be delayed in some cases of jaundice and not in others. Whipple has found that in cases of jaundice associated with liver disease there may be a reduction of the fibrinogen of the blood.

The danger of hemorrhage following operation on jaundiced patients is well known, and further study of the blood in this condition may furnish a means of determining in advance those cases in which bleeding may prove a troublesome feature and those in which no danger may be expected from this source.

At present a delayed coagulation and bleeding time are usually taken as an indication of danger. In such cases prophylactic injections of serum may be tried, and if the coagulation and bleeding time return to normal operation may be performed with little fear of hemorrhage. If hemorrhage occurs spontaneously or following operation in a jaundiced patient serum injections may be employed, and there are numerous reports of favorable results attending their use. Transfusion may be necessary in the graver cases of hemorrhage. Cases with deficient fibrinogen would probably be influenced favorably only by the introduction of whole blood.

Diseases of the Liver.—Whipple and others have found a deficiency of fibrinogen in a variety of diseases of the liver with and without jaundice. It is unlikely that the primary disease in any of these cases could be influenced by the methods here considered. In the case of hemorrhage it seems unlikely that injections of serum or of defibrinated blood would be of value, since neither of these agents contains fibrinogen. It would be more rational in such cases to introduce whole blood.

Metrorrhagia.—Favorable results have been reported by Busse from the use of serum injections in metrorrhagia occurring under various conditions.

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CHAPTER IV

THE FUNCTIONAL ANALYSIS OF ANAPHYLAXIS

John Auer

Introduction.—One of the most important modern contributions to our knowledge of functional disturbances has been the development of the conception called anaphylaxis, or protein hypersensitiveness, and on its basis insight has been gained into many puzzling processes, especially in the so-called idiosyncrasies. Any living structure of the organism apparently may be the seat of direct or indirect anaphylactic changes, and these changes manifest themselves according to the nature of the structure affected, which may be, for example, the skin, the respiratory tract, the circulatory apparatus, or the gastro-intestinal canal and its various glands. This variety of effects and affected structures makes the study of anaphylaxis of great value to the physiologist, pharmacologist, and to the modern clinician. But this diversity of effect emphasizes an important point in our conception of anaphylaxis, and that is that anaphylaxis is not a clinical entity on account of its manifestations, like outspoken cases of lobar pneumonia, acute articular rheumatism, or exophthalmic goiter, which are diagnosed by a series of well-defined symptoms and signs, but that anaphylaxis is an entity only when viewed as to its primary causation.

The various theories and theoretical applications of anaphylaxis will be touched but lightly. No attempt will be made to give an exhaustive survey of the subject, but attention will be paid chiefly to the functional changes which anaphylaxis calls forth in the animal organism, for such alterations are the phenomena which the clinician meets in his daily work. As a large part of our information has been gained through animal experimentation, much of what follows will deal with the lower animals, because only in them could the investigator carefully and laboriously study the origin of the disturbances produced. While caution must undoubtedly be exercised in transferring the results gained by animal experimentation to the explanation of similar derangements observed in man, it is not premature to state that many, if not all, the typical anaphylactic phenomena observed in the guinea pig, rabbit, and dog apparently find their counterpart in man.

The restriction in the scope of this article is permissible because a number of excellent general reviews and presentations of special viewpoints are available to the student (see References).

History.—Like all advances in science, the conception of anaphylaxis was foreshadowed many years ago. According to Morgenroth, the famous French physiologist Magendie noted that rabbits tolerated an intravenous injection of egg-albumin, but succumbed when the injection was repeated after an interval of days. A similar observation was made by Flexner in 1894, who found that rabbits survived the intravenous injection of dog serum, but died when the same serum in the same amount was again injected after an interval of days or weeks. The observations of Behring in 1893 are also of interest in this connection, although their identity with anaphylaxis is not yet fully established. Behring observed that horses, sheep, and goats, which had been immunized with diphtheria toxin or tetanus toxin, became in time so sensitive to the injection of the substance that they succumbed to a small fraction of the dose which normally caused only a transitory reaction; at the same time it was demonstrated that their serum showed a higher content of antitoxin.

Similar and still more striking results were observed by other investigators in guinea pigs. In spite of the interest of these observations the existence of a new principle was not suspected and the subject became important only after the researches of Richet, Arthus, von Pirquet and Schick, Theobald Smith, Otto, and Rosenau and Anderson.

The researches of Richet and his collaborators, which began as early as 1902, brought out a number of valuable facts. He used water extracts of the tentacles of sea anemones, actinia and mussels, and also a vegetable toxalbumin, crepitin. Although all these extracts were poisonous, and in proper dosage caused death, Richet found that sublethal doses, which produced but mild symptoms in normal dogs, would elicit violent effects and death when injected intravenously into dogs which had received a similar injection two or three weeks previously. A cumulative action of the poison was excluded by the observation that a reinjection after three to five days produced only a moderate effect. Moreover, Richet discovered that normal dogs could be rendered highly sensitive to these extracts if they were first injected with the blood of animals which previously had been injected with these substances. There was, therefore, something in the blood of treated animals which transmitted this state of increased susceptibility to the action of the poisonous extracts. These experiments showed not only that a certain time was necessary between the injections before the animal would exhibit this enhanced reaction, but also that a state of increased and transmissible susceptibility to the action of the extracts had developed. In order to emphasize this, and to bring out clearly the point that the injected animal had not developed an increased resistance to the injected substances, but on the contrary had become more sensitive to it, Richet coined the word anaphylaxis.

The symptoms observed were briefly as follows: The reinjected dog shows within a few seconds dyspnea, vomiting, general weakness, and diarrhea; associated with this is a strong drop in blood-pressure (Richet). Death occurs in a large percentage of the dogs within one hour after the reinjection. Similar effects were also seen in rabbits which had been previously injected with actinia extract. He also noted that the animals reacted most strongly when the same extract was injected which was employed the first time.

The most important facts contributed by Richet were that the injection of dogs and rabbits with small, almost harmless doses of poisonous albuminous extracts produces, after a definite and necessary interval, a state where the injection of the same dose causes an immediate, violent intoxication which often leads to death. This state of hypersensitiveness, or anaphylaxis, could be transmitted to normal animals by injecting them with the blood of dogs which had previously been treated with the extracts.

Richet's experiments, however, were complicated by the material he employed. Because the extracts utilized contained both a toxin and a protein, his animals showed at the same time an immunity to the toxin due to antitoxin formation and a hypersensitiveness due to the proteid portion of the extract injected. On reinjection, therefore, Richet sometimes observed that the prepared dogs showed an initial intense effect, but nevertheless survived, although the dose was so large that normal dogs invariably succumbed.

This complication of the experimental result which Richet's work shows was avoided by Arthus, to whom we owe the first physiological investigations in anaphylaxis produced by the injection of a non-toxic serum. He demonstrated that horse serum,[1] fresh or preserved, heated to 57° C., or unheated, could be injected subcutaneously, intraperitoneally, or intravenously into rabbits without causing any immediate or remote accidents. If these injections are repeated every six days, however, the rabbit sooner or later reacts with a pronounced and striking skin reaction if the injections are given subcutaneously or with more or less profound general symptoms when the last injection is given intravenously. Arthus also noted phenomena of anaphylaxis in the guinea pig and the rat after they had been injected repeatedly with horse serum. He was also able to produce similar effects when milk or egg-albumin was used instead of horse serum.

Arthus was the first to show that an originally harmless protein may produce grave toxic symptoms, and even death, when injected repeatedly at certain intervals into an animal, but he did not regard these reactions as specific (Arthus).

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[1] The horse sera used by Arthus were the antitoxins for diphtheria, tetanus and snake venom.

Shortly after the first publication of Arthus, von Pirquet and Schick reported the results which they had obtained when rabbits were reinjected with horse serum. Their investigation was undertaken in order to gain an insight into the causation of the morbid changes which sometimes occur in man after the injection of diphtheria antitoxin, for example, fever, urticaria, edema, painful swelling of the joints, etc. In 1905 a monograph appeared by the same authors dealing with these complications which the authors call serum disease (von Pirquet and Schick). In 1903 Theobald Smith made his first observations of the phenomenon which was later to bear his name. During the routine examination of diphtheria antitoxin to detect any possible bacterial contamination, and to determine its antitoxic titer, Smith noted that guinea pigs which had survived the injection of a diphtheria toxin-antitoxin mixture frequently died within a few hours when the antitoxin was again injected. For normal guinea pigs, that is, pigs which had never before been treated with antitoxin or with toxin-antitoxin mixtures, the injection of antitoxin was nearly always harmless.

Theobald Smith's observations were fully corroborated and amplified in 1906 by Otto, and independently by Rosenau and Anderson. Otto investigated the "phenomenon of Theobald Smith" at the request of Ehrlich, whose interest in the subject had been aroused by a conversation with Theobald Smith in the latter's laboratory. Rosenau and Anderson investigated the question in order to gain information about the cause of sudden deaths which now and then occur after the administration of diphtheria antitoxin in the human being.

These important researches roused general interest and ushered in the general experimental study of anaphylaxis, for investigators now had a definite procedure and a highly suitable animal, the guinea pig, at their disposal.

EXPERIMENTAL ANAPHYLAXIS

The term "anaphylaxis" is employed in this article in the following sense: It is used as a group name for those alterations of function and anatomical changes which occur when an animal is reinjected after an appropriate interval with the same protein solution; these alterations must not be obtained, or at least not to the same degree, when the same dose of the protein is injected into a normal animal. Attention must be called at once to the important fact that the reactions observed in the anaphylactic animal are not in themselves diagnostic, for similar and even identical reactions may be observed in normal animals after injecting them for the first time with a large number of widely different substances; but these reactions, when they occur for the first time as the result of a definite procedure, namely, reinjection of the same protein after a definite interval, are then absolutely characteristic of anaphylaxis.

The term "anaphylaxis" is employed by some to designate the sensitized state, that is, the condition after the animal has been injected for the first time with some foreign soluble protein. Still others use the term to describe both the sensitized state and the symptoms of intoxication which result from the second injection of the alien protein. This fluctuating value of the word "anaphylaxis" introduces some confusion, and in the interest of precision it would be desirable to use the terms "anaphylactic reaction" and "anaphylactic sensitization" more generally than has been done so far; as a group name, the term "proteinization" is often convenient for designating animals which are in various states due to the action of an alien protein: for example, a proteinized group of animals may contain members who are sensitized, in a refractory state, or who are undergoing or have survived an anaphylactic or a non-specific protein reaction.

Active Anaphylaxis.—The fundamental guinea-pig experiment in anaphylaxis will make the above statements clearer. If a normal guinea pig is injected with a small quantity of normal horse serum subcutaneously, intraperitoneally, or intravenously the animal hardly shows any discomfort during the injection or at any time afterward, and is in no way distinguishable from its normal mates.[2] The first injection thus causes no obvious ill effect and has apparently produced no harm, and yet profound alterations have taken place which appear under specific and non-specific conditions. If this treated or sensitized animal is reinjected with the same horse serum after the lapse of several weeks it now responds with striking symptoms and signs, and may even succumb. The horse serum, which was apparently harmless on first injection, has now acted like a violent poison when injected for the second time. Qualitatively different, but just as marked symptoms may also be observed in properly prepared rabbits and dogs when the same protein is injected for the second time. This transformation of a harmless substance into a violent "poison" can, however, be observed only if a proper time interval separates the two injections. If the injection is repeated after three or four days, no immediate ill effects are observable, the animal behaves like a normal individual.

The non-specific alterations which the parenteral introduction of an undenatured alien protein calls forth are only imperfectly known. These reactions and their potential dangers will be considered later.

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[2] That important changes occur in the liver after simple sensitization has been noted in the guinea pig by Hashimoto and Pick; these changes, however, bear no direct relationship to the anaphylactic reaction (see also page 89).

We therefore can distinguish three steps in the production of anaphylaxis: (1) sensitization; (2) incubation; and (3) intoxication. These steps may now be considered in more detail.

SENSITIZATION

Sensitizing Substances.—All the substances, or antigens, which have been shown to sensitize an animal belong to the protein group. It may be said that any soluble foreign protein, of animal or plant origin, may sensitize if it reaches the circulating juices of an animal in an unaltered native state, so that the characteristic structure of the protein is preserved.

The following list, quoted from Doerr, will illustrate the variety of substances which have been tested:

I. Animal proteins in solution:

1. Foreign serum and its derivatives produced by salting out, by heating, by iodizing, etc.
2. Hemoglobins.
3. Milk (casein, lactoglobulin, lactalbumin).
4. Egg-albumin (ovovitellin, ovomucoid, ovalbumin).
5. Extracts of organs, tumors, mummies, or of entire animals like oysters, mussels, trout, insects, tenia.
6. Sweat, bile, albuminous urine, gastric juice, expired air of human beings.
7. Fluid contents of echinococcus cysts.
8. Snake venoms.
9. Ferment solutions containing proteins: papain, rennin, papayotin, pancreatic juice, trypsin.
10. Nucleoproteins from organs.

II. Cellular animal proteins:

1. Red blood-corpuscles.
2. Leukocytes.
3. Spermatozoa, ova.
4. Syncytial cells.
5. Cells of organs and tumors.

III. Vegetable proteins in solution:

1. Extracts of bacteria, yeast and other fungi.
2. Bacterial nucleoproteins.
3. Albuminous extracts of seeds.
4. Purified or pure vegetable proteins like excelsin, gliadin, hordein, zein, vignin, etc.
5. Crude vegetable fats and oils (always containing proteins).

IV. Cellular vegetable proteins:

1. Living or dead bacteria, yeasts, schizomycetes.
2. Pollen granules.

The most commonly employed anaphylactic antigens (anaphylactogens) are horse serum, bovine serum and egg-white. When these agents are used experimentally it must be clearly realized that they represent mixtures of anaphylactogens, for each one contains several distinct proteins of which each one sensitizes. One may agree, therefore, in general with the emphatic statements of Doerr and of Wells that greater progress, at least in certain directions, would be achieved if chemically pure proteins were employed more extensively in research, for the rivalry of the various antigens in the mixture introduces complications which may obscure the interpretation of results.

Dosage for Animals.—Exceedingly minute quantities of a foreign protein suffice to induce sensitization. Rosenau and Anderson obtained in one instance sensitization in a guinea pig with 0.000,001 c.c. of horse serum; and Wells showed that crystallized egg-albumin in a dose of 0.000,000,05 gm. could still render a guinea pig susceptible. Such infinitesimal quantities, far beyond the range of any balance or test-tube reaction, are not the most favorable doses for the production of a constant and high grade of sensitiveness. General experience has shown that larger doses are necessary in order to obtain marked symptoms on reinjection. The doses vary with the animal species employed, for these show considerable differences in the ease with which sensitization is secured. The most susceptible laboratory animal is the guinea pig, and a single injection of alien serum varying from 0.01 to 1.0 c.c. sensitizes it so highly that the animal usually dies when the second injection is given intravenously after an appropriate interval.

Rabbits are not so easily prepared, nor can a high degree of sensitization be obtained as readily and as certainly as in guinea pigs. A modification of the procedure introduced by Arthus probably gives the best results. Arthus injected his rabbits repeatedly (four to eight times) with 5 to 10 c.c. of foreign serum; the injections were separated by intervals of four to eight days, and were usually given subcutaneously; sometimes, however, also intraperitoneally. Such rabbits apparently always showed some noticeable reaction when reinjected, and a certain percentage died acutely. Excellent results may be obtained if a not too small series of young rabbits is injected repeatedly at about five-day intervals with 2 to 3 c.c. of horse serum. The injections are given subcutaneously, intraperitoneally, and intravenously in turn, so that each rabbit receives serum by all three routes (Auer). The injections should not be less than four in number. During the process the rabbits require watchful care, as otherwise a number of them are certain to die of respiratory diseases

There are other methods for the preparation of rabbits described by Friedemann, Friedberger, and Scott, not reported here, for apparently no method will invariably give a high degree of sensitization in all rabbits; there are always animals which give but a slight or no reaction when the test is made. For this reason it is best to prepare not less than twelve animals; in such a series all gradations of the anaphylactic reaction will probably be obtained on reinjection.

Dogs may be readily sensitized by a single subcutaneous injection of 3 to 5 c.c. of foreign serum (Biedl and Kraus). Arthus injected 10 c.c. serum six to eight times at seven-day intervals. A subcutaneous injection of 10 c.c. alien serum in two places, each receiving 5 c.c., yields an excellent sensitization as a rule.

The guinea pig, rabbit, and dog are the animals whose reactions have been studied most carefully, but they are not the only animals which can be sensitized. References in the literature indicate that horses, goats, sheep, pigs, cats, opossums, rats, white mice, pigeons, chickens, geese, ducks, and frogs are sensitizable. That man is sensitizable seems indicated by von Pirquet's and Schick's studies; by the occurrence of sudden death in chronic asthmatics after the administration of a therapeutic serum, and by the development of apparently typical anaphylactic reactions in individuals reinjected with the same serum after a period of incubation. This view that man is sensitizable is denied by Coca who states that there is no evidence that the protein antigens act as anaphylactogens in the human subject. The suggestive inference of Coca has been critically analyzed by Doerr in his latest review; he comes to the conclusion that idiosyncrasy, anaphylaxis and tuberculin hypersensitiveness are to be considered members of the same general system of alterations.

Methods.—While the chief, because the most certain, method of producing experimental sensitization is the injection of foreign protein either subcutaneously, intraperitoneally, or intravenously, there are other procedures for achieving this result which are of great theoretical importance. Thus sensitization may be *inherited,* for the susceptibility to a foreign protein is transmitted from the mother guinea pig to her young, as Rosenau and Anderson showed in their first publication in 1906; Cooke and Van der Veer have recently investigated this problem thoroughly. Sensitization may be established by *feeding* guinea pigs dried horse serum, and dried or fresh horse flesh (Rosenau and Anderson); or by feeding raw cow's milk (Kleinschmidt); or perhaps even by the *instillation* of one drop of normal horse serum into the intact conjunctival sac (Rosenau and Anderson), though this has not been corroborated by Colombo. *Inhalation* of serum produces a specific sensitization, according to Busson, Rosenau and Amoss, Friedberger, Sewall, and others. *Inunction* of horse serum-lanolin salves into the intact or scarified skin of guinea pigs produces sensitization, according to Clough. The same author also sensitized guinea pigs by repeatedly injecting mixtures of horse serum and gum arabic into the vagina or rectum of guinea pigs. That sensitization may be accomplished by these procedures is of value in explaining those cases in the human being where the first injection of an antitoxin produces a more or less severe anaphylactic reaction. The experimental proof that sensitization may be inherited or brought about without any injury of the mucous or serous membranes or the skin is of importance in the endeavor to explain certain so-called idiosyncrasies of man.

Specificity.—When an animal has been sensitized with a certain foreign protein, horse serum for example, a reaction is only obtained when the animal is reinjected with horse serum; the injection of rabbit or goat serum is without effect (Otto, Rosenau and Anderson).

This specificity of the reaction is outspoken and sharp when proteins of widely different species are chosen, but there are group reactions when proteins of closely related species are employed. Thus Rosenau and Anderson report that guinea pigs sensitized with hen egg-white react to a subsequent injection of duck egg-white or vice versa. The anaphylactic reaction is therefore specific in the same sense that hemolysins, agglutinins, and precipitins are specific. These group reactions have been especially studied by Wells and Osborne. These investigators used in their experiments the purest plant proteins ever employed. They found, for example, that guinea pigs sensitized with gliadin from wheat or rye give a strong anaphylactic reaction with hordein from barley, but this reaction is not as marked as if the homologous protein had been employed. Similar results are obtained if the sensitizing protein is hordein and the second injection is gliadin. As these two substances are chemically distinct though similar proteins, Wells and Osborne believe that the specificity of the reaction is determined by the chemical constitution of the protein rather than by its biological origin.

Recent investigations have shown that the same antigen may produce different types of antibodies. If the injected amount of antigen is small, antibodies of marked specificity are produced by the cells of the organism. If the amount injected is large, or a small amount is repeatedly incorporated, then the specificity of the produced antibodies is diminished and group reactions now occur when the tests are made.

There is another form of specificity which must be briefly touched. In 1904 Wolff-Eisner found that sensitization may be produced by organs. This organ specificity is especially pronounced in the crystalline lens of the eye. Uhlenhuth established that lens protein produces precipitins which act specifically upon the lens proteins of all animals, and not only upon the special lens protein used for the production of the precipitin; also that these precipitins affect no other protein. For the anaphylactic reaction Kraus, Doerr and Sohme, among others, demonstrated that rabbits sensitized with bovine serum do not react to bovine lens extracts, and that rabbits prepared with bovine lens extracts react only to lens extracts, but not to bovine serum. This biological differentiation may be great enough that guinea pigs can be sensitized with the crystalline lens of their own eye and the anaphylactic reaction obtained later by injecting an extract of the lens of the other eye (Uhlenhuth and Händel; see also Römer and Gebb and Kapsenberg).

Another example of organ specificity is shown by the behavior of blood serum and red blood-corpuscles of the same animal. Guinea pigs prepared with serum are only slightly, or not at all, sensitized to the homologous red blood-corpuscles, and vice versa (Thomsen).

Investigations with liver, kidney, spleen, thymus, and brain tissue, also indicate that their proteins differ from that of the serum, and are capable of sensitizing an animal. There are, however, observations which show that a serum used for sensitization and intoxication may give active cross reactions with organ proteins (Pearce, Karsner, and Eisenbrey).

Regarding the organ specificity of the placenta, the statements in the literature directly contradict one another. Some affirm and others deny that sensitization and subsequent intoxication of an animal can be effected by extracts of placental tissue from the same species. A similar condition prevails with regard to fetal serum.

Influence of Various Manipulations on Sensitizing Substances.—That the sensitizing property of protein is very resistant has been demonstrated by Rosenau and Anderson, and by Wells, among others. Drying and redissolving, heating to 60° C. for six hours, precipitation by ammonium sulphate and dialysis, or the addition of iodin, had no effect on the sensitizing property of horse serum. The sensitizing property disappears almost entirely, however, when horse serum is heated to 100° C. for one hour. Peptic and tryptic digestion destroys the sensitizing power slowly, and sensitization may still be obtained with solutions which show no coagulable albumin. Cleavage products of the proteins, however, do not in general sensitize; even the change of crystallized egg-albumin into acid albumin weakens, and the change into alkali-albuminate destroys the sensitizing property entirely. Full details will be found in Fink's review, also in that of Schmidt.

Non-specific Alteration of Animal Organism Sensitized with Foreign Protein.—In addition to the specific changes which the animal undergoes as the result of a primary parenteral injection of an undenatured, soluble foreign protein, there are other non-specific alterations in reactivity which may be detected and which are of considerable interest. Heilner in 1908 noticed that serum-sensitized rabbits succumbed to an injection of 4 per cent sodium chlorid which was practically harmless to normal controls. Davidsohn and Friedemann showed that rabbits sensitized with bovine serum react with temperature elevations to subcutaneous or intravenous doses of sodium chlorid which produce no such effect in normal rabbits.

Richet observed that dogs sensitized by actinocongestin or crepitocongestin vomited after smaller doses of apomorphin hydrochlorid, injected intraperitoneally, than normal dogs. Recently Auer and Witherbee have demonstrated that rabbits sensitized with horse serum may develop a tremendously increased resistance of the skin to doses of X-rays which are surely destructive to the skin of normal controls, controls sensitized after X-raying or to sensitized and reinjected rabbits. The same authors furnish evidence that the protection is apparently due to the locally anchored anaphylactic reaction bodies.

These non-specific reactions described above are probably only a few of those which occur after sensitization with an alien protein and further research may disclose many more. In this connection Auer and Witherbee suggest that some of the erratic fluctuations in reaction frequently observed in a series of supposedly normal animals of the same species, may have their cause in an unsuspected proteinization of the abnormal reactors; should this hypothesis prove true, a method would be available to enrich our knowledge of non-specific reactions.

Since mere sensitization with an alien protein alters the reaction of the organism not only towards this protein itself, but also towards an unknown number of other unrelated substances or even physical agents, it is obvious that proteinized animals cannot serve as normal controls until it has been demonstrated that both react to the same agent in the same manner and to the same degree. This precaution has not been taken by many investigators and this failure may perhaps explain the discordant results obtained in diverse studies of the same problem. For the therapeutic use of non-specific reactions the review of Jobling may be consulted.

Incubation

The period of incubation is the time interval which elapses before the injected animal shows symptoms when reinjected with the same protein. It represents the length of time which the body requires for altering certain reaction capacities, so that the reinjection of seemingly harmless protein now acts like a violent poison. If the reinjection is given too early no noticeable effect is obtained, and the animal behaves apparently like a normal individual. This condition of sensitiveness develops gradually, reaches a maximum, and then diminishes again in some species, while remaining more or less constant in others.

The duration of the period of incubation before sensitization is established depends largely upon the animal species and the method of test, and to a less extent upon the quantity of soluble foreign protein injected for the first time, or to the site of injection.

Ranged in order of sensitiveness we have: (1) guinea pig; (2) man (Doerr); (3) rabbit; (4) dog. In the guinea pig the period of incubation is about ten days (Rosenau and Anderson, Otto); in man seven to twelve days (von Pirquet and Schick);[3] in the rabbit eight to fifteen days after the last injection (Arthus); in the dog two to four weeks (Biedl and Kraus).

Small doses of the protein, less than 0.0001 c.c. horse serum, delay the development of sensitization, and large doses, over 10 c.c. horse serum, appear to exert the same effect. Heating the protein to 80° C., or any method which partly denatures it, delays the onset of sensitization.

The site of injection exerts some influence, but it amounts to only a few days' difference. If medium doses are employed for sensitization the periods of time given above will be found fairly accurate.

After sensitization has been developed this state may continue for a greater or less period of time. Anderson and Rosenau report that guinea pigs sensitized with a single injection of horse serum remain sensitive during life, which is about three years; the degree of sensitization, however, is considerably decreased after three years, so that five to ten times the original lethal dose is then merely toxic and does not kill (Auer). In human beings apparent anaphylactic symptoms have occurred when serum was reinjected about five years and longer after the first injection (Currie, Goodale, Darling). In the rabbit acute death may still be obtained four to six weeks and longer after the last sensitizing dose (Arthus' method). Scott, however, reports that sensitization disappears in the rabbit soon after the twentieth day. In the dog also sensitization may persist for weeks and months, after a single sensitizing dose of horse serum; in one surviving dog Auer obtained the typical blood-pressure effect one year after sensitization.

INTOXICATION

When a sensitized animal is reinjected with the same sensitizing protein, various functional disturbances occur which did not appear when the substance was first injected. These disturbances, while they show certain resemblances in the different animal species, disclose marked differences in the way the symptoms are combined and in the degree of functional alteration which predominates. The symptoms vary with the method demonstrating the state of sensitiveness, and they vary also according to the degree of sensitization the tested animal has attained or retained.

The most obvious symptoms and anatomical changes which occur during the anaphylactic state, both acute and subacute, are fairly constant for each species with a given procedure for reinjection of the protein. This picture does not vary with the nature of the proteins employed, but all proteins, irrespective of their chemical nature and derivation, cause the same anaphylactic alteration in the same species: anaphylaxis produced by horse serum is identical with that produced by edestin, a protein from hemp seed. There is but one, perhaps complex, anaphylactic picture for each species, but it is developed by a large number of different substances, which, however, all belong to the protein group.

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[3] For the present, serum disease may still be classed among reactions which are at least closely related to anaphylaxis, even if the process is not wholly identical with that observed and analyzed in the lower animals.

Symptoms.—In general it may be said that respiratory disturbances characterize the acute anaphylactic intoxication in the guinea pig; circulatory changes in the rabbit; gastro-intestinal and circulatory alterations are most prominent in the dog, while man shows marked skin lesions in the majority of cases, though respiratory and circulatory changes also occur. A fairly detailed description of the symptoms and their analysis will be given later.

Method—*Dosage.*—The intoxicating dose of the protein may be administered in the same variety of ways with which sensitization is produced. The main methods are by subcutaneous, intramuscular, intraperitoneal, and intravenous injection. For quantitative work where it is necessary that differences in the rate of absorption be avoided, the intravenous route is imperative. The vein chosen in guinea pigs is the external jugular; in the rabbit the lateral ear vein or the jugular; and in the dog the saphenous or the jugular vein. The intracardiac method is not to be recommended as a substitute for the intravenous injection; it is easy to attempt in the guinea pig, but serious damage to the heart is by no means rare. Intoxication may also be caused by subdural, intracerebral, and intraspinal injections; by inhalation, or by injection of the protein intratracheally.

While the quantity of foreign serum necessary to produce symptoms on reinjection varies with the site of injection, and with the criteria adopted, it is much larger than the amount which sensitizes. In the guinea pig, for example, which has been sensitized with horse serum it is probably impossible to give a dose subcutaneously which kills with certainty. Lewis states that 5 to 6 c.c. subcutaneously always gives a well-marked reaction, so that 15 to 20 c.c., if absorbed at the same rate, would be fatal. When the reinjection is given intraperitoneally 5 to 6 c.c. kills; and the fatal dose is still smaller with intravenous reinjection. To kill highly sensitized guinea pigs 0.01 to 0.02 c.c. may be sufficient. Both in the rabbit and dog acute exitus cannot be obtained when the foreign protein is injected subcutaneously, due undoubtedly to the fact that the protein is absorbed too slowly, and thus it never reaches a sufficiently high concentration in the blood. Figures given by Doerr and Russ show this difference between the amount of the sensitizing and intoxicating doses; they furnished evidence that the minimal sensitizing dose in the guinea pig is 200 to 2,000 times smaller than the quantity of the same protein which causes symptoms or acute death when injected intravenously.

Sensitizing and Intoxicating Substances of Foreign Protein.—Largely through the work of Rosenau and Anderson, Doerr and Russ, and Wells, it is generally accepted that the sensitizing substance and the substance producing the anaphylactic symptoms are identical. The evidence, however, is not absolutely conclusive, although it seems certain that the protein molecule as a whole exerts both of these functions. The work of Vaughan and his collaborators, for example, indicates that all true proteins can be split into a toxic and a non-toxic fraction by heating the protein a few hours at 78° C. in a 2 per cent solution of sodium hydrate in absolute alcohol. The toxic fraction kills guinea pigs with symptoms which resemble those observable in anaphylactic animals, but it cannot sensitize. The non-toxic fraction, however, usually sensitizes, but the sensitization is specific only for the entire protein molecule, and not for the non-toxic portion itself. These experiments suggest that a separation of the sensitizing and intoxicating principles is apparently possible.

THE ANAPHYLACTIC REACTION

General Symptoms

Guinea Pig.—The symptoms obtained when a sensitized animal is reinjected with the same protein vary considerably in the different species, though the difference on analysis is probably largely a quantitative one. Moreover, the probability also must be considered that the anaphylactic reaction picture we possess is not complete, and that in all likelihood there are numerous anaphylactic reactions of which we as yet know nothing.

After a sensitized guinea pig has received an intravenous injection of the foreign protein, and is then liberated, the animal remains quiet for about a minute, and then restlessness appears. It moves about, the hairs bristle over the neck, head, and body; it sneezes frequently and sits up on its hind legs to rub its nose vigorously; occasionally the animal seems startled, and makes a sudden, small jump. Within two or three minutes the animal is unable to stand, falls on its side, and violent tonic and clonic convulsions develop. In the intervals between convulsions the animal lies motionless on its side; the legs are neither spastic nor flaccid, and a pinch of the toes usually elicits a vigorous kick. Respiration during this stage is slow and labored, and may cease for a short time. The final stage is ushered in by a group of respirations, which swiftly get weaker, and finally stop entirely. The entire process need last no longer than three minutes. The heart on palpation usually beats vigorously and regularly, though slowly, and continues to beat for some minutes after all respiration has entirely stopped.

This picture is completed if another experiment is made with a sensitized guinea pig stretched out on its back. After recovery from the ether anesthesia employed to introduce a cannula into the jugular vein, the toxic or second injection is given through this cannula, and the cannula then washed clear by 1 or 2 c.c. of saline or Ringer solution. Within thirty seconds the respirations quicken noticeably for a short time, and the animal struggles and squeaks shrilly. Careful inspection now shows that the respiration is slower, and that the thoracic wall, especially the costal margin, sinks in with each inspiration. This rhythmic inspiratory depression of the chest wall increases more and more, and the respirations become still slower, but much more powerful and labored. At this stage, especially in young animals, one may see that the lower part of the sternum and costal margins are drawn inward to an astonishing degree with each inspiration. Now tonic and clonic convulsions develop, accompanied by no sound, or, at most, by a choking, feeble squeak; the pupils dilate; the mucous membranes of the mouth appear bluish; there is often a spurt of urine, and a number of normal fecal beans are passed. The convulsions cease after a short time, and the animal lies motionless without any respiration, but the heart is seen beating with strong, slow, regular pulses; the chest looks fuller than normal; and there may be active peristalsis, which is easily visible through the relaxed abdominal walls. After a respiratory stoppage of about one minute, which may be broken by an occasional inspiration followed by a convulsive active expiration, a group of respirations appears. This terminal group is formed by respirations which are at first slow and of fair strength, but rapidly become swifter and weaker, and finally disappear about one minute after their onset. Each of these terminal respirations is preceded by a dilatation of the nostrils and an opening of the mouth, which is maximal at first; as the respirations weaken the opening of the mouth and the dilatation of the nostrils decrease, and they also disappear. The order of stoppage is first the thoracic respiration, then the opening of the mouth, and finally the inspiratory widening of the nostrils. Cessation of respiration is now permanent. At this time the heart still beats regularly and strongly, though apparently at a slower rate than during the respiratory stoppage, and its beating usually continues for many minutes after respiration has permanently ceased.

The striking symptoms just described for the guinea pig appear when the injected animals are highly sensitized and when a lethal dose is given intravenously. If the test animal is not highly sensitive, or if the dose injected is sublethal, the picture may show all gradations from the fatal type described to mild effects chiefly characterized by restlessness, sneezing (coughing?), erection of the hair, moderate bucking movements, and discharge of feces and urine. It is interesting and instructive that animals which show a most severe reaction may nevertheless apparently fully recover after an hour or two, and feel well enough to fight with their neighbors. On the other hand, there is also a protracted course of the intoxication[4] which leads to death after some hours. In these animals paralytic symptoms are the most noticeable because the most lasting.

Rabbit.—In this animal the anaphylactic reaction reveals itself either as a local or a general manifestation, depending upon the method of reinjection of the foreign protein.

The general reaction is obtained when a highly sensitized rabbit is reinjected intravenously with the foreign protein. The respiration quickens at first and the animal lies down upon its belly for a time, often with the hind legs extended backwards; a greater or smaller number of dry normal fecal pellets are passed. Within a few minutes, however, the respiration slows, and the animal suddenly falls over on its side with clonic convulsions of short duration. The head is retracted strongly, the iris vessels (easily seen in white rabbits), gums, and tongue are pale, the pupils are wide. The convulsions are sometimes preceded or accompanied by a few feeble, shrill cries. After the convulsion the animal lies motionless without respiration, and immediate palpation of the chest, as a rule, fails to detect any cardiac pulsation. After less than one minute the terminal group of gradually weakening respirations appears; as in the guinea pig, these are preceded and accompanied by an opening of the mouth. The animal now shows no visible or palpable heart beats or respirations; it is perfectly relaxed, and the abdominal walls bulge when the animal is placed on its back. As a rule, one sees now very active peristalsis and antiperistalsis of the cecum, which is sharply outlined by the relaxed abdominal parietes. The time interval between injection and terminal group of respiration need not exceed three minutes. It is deserving of notice that the respiration of the rabbit during this reaction is never dyspneic.

A reaction of this fulminant character cannot be obtained with the same certainty in the rabbit as in the guinea pig. In the latter animal over 95 per cent of a series prepared and reinjected with an adequate dose will succumb; in the rabbit, however, only a number of a series prepared in exactly the same way will succumb acutely as described above. The others show on inspection rapid respiration without group formation, as in the normal rabbit; more or less marked discharge of normal scybala; often erection of the hair of the body; a temporary but well-marked miosis of the pupil, usually lasting for some minutes. During the stage of polypnea the animals lie quietly on their belly with the head moderately retracted and often with the hind legs extended. Within half an hour or less after the reinjection the animal may seem perfectly normal.

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[4] The word intoxication is used merely as a descriptive term and does not postulate the existence of a true toxin or toxins as the cause of the anaphylactic reaction.

In animals which recover from an intravenous reinjection Arthus describes a gradually developing cachexia, accompanied by a diminution in the number of red corpuscles and a lowered hemoglobin content. This cachexia, Arthus states, leads to death in a few weeks. Such a cachexia does not develop in guinea pigs which survive an intravenous injection; they have been found in excellent condition over a year after a very severe reaction.

The *local reaction* appears when a sensitized rabbit is reinjected subcutaneously, and constitutes the well-known phenomenon of Arthus. Arthus describes the process as follows: If a rabbit is sensitized by the subcutaneous injection of 5 c.c. of horse serum every six days, the first few injections will be absorbed in a number of hours. The fourth injection usually produces a soft infiltration which is not absorbed before two or three days have passed. The fifth injection causes an edematous infiltration which is harder, and is not absorbed before five or six days. The sixth injection rapidly produces a white, solid, compact, subcutaneous mass which is not pus, and which may persist for weeks. Similar but more pronounced changes are obtained on the seventh injection of 5 c.c. of horse serum: the skin over the subcutaneous mass becomes red, then pale, and begins to harden, and a spot of gangrene develops which produces a refractory wound. The general condition of the animal, however, remains excellent.

These local phenomena are not due to the repeated injection of the foreign protein into the same locality, because they are also obtained when each subcutaneous injection is given in a different place, or when all injections except the last have been intraperitoneal. This last injection, however, must be given beneath the ventral or thoracic skin if the typical phenomena are to be produced; injection beneath the skin of the ear, for example, produces only a voluminous edema, according to Arthus. The quantity of protein, horse serum in Arthus' experiments, played no apparent rôle; less than 1 c.c. at each injection produced the same tissue changes as 10 c.c.

These local lesions, as well as the cachexia noted by Arthus in surviving rabbits, Coca is inclined to attribute to a circulatory deficiency caused by a contraction of the arterioles. That such postulated local vascular constrictions do occur in various parts of the body during an anaphylactic reaction has been shown by Schultz and Jordan, Fröhlich, Auer and by Huber and Koessler.

A similar local reaction (phenomenon of Arthus) may also be obtained in the guinea pig (Lewis) if the animals do not die before its development. In the dog, Arthus was unable to obtain this local reaction; after seven subcutaneous injections of horse serum at seven-day intervals the last dose was entirely absorbed within four to five hours, and no change was observable during the next three days at the site of injection.

Dog.—This animal, when not anesthetized, also exhibits striking symptoms, chiefly gastro-intestinal, during the anaphylactic reaction. The following description is based largely upon the descriptions of Biedl and Kraus, and Richet. If a sensitized dog is reinjected intravenously with the same protein used for sensitization, the animal shows a marked excitement within one minute, often before the injection is finished. The stage of excitation does not last long, and the animal begins to make swallowing motions. Soon retching develops, followed by vomiting. The vomitus, according to Richet, may be bile-stained, bloody, or even fecal, and vomiting occurs even though the animal is fasting. While vomiting the animal is usually able to stand, but nevertheless exhibits the marked muscular weakness usually associated with true vomiting. Associated with the vomiting, which occurs repeatedly, there may be fecal discharges. The animal now usually lies or rather falls down, and remains quietly in the same position, breathing without difficulty. At no stage is there any noticeable dyspnea. The dog may now die or slowly recover within the next few hours. According to Biedl and Kraus, the corneal reflex is always present, and the animals react to stimulation of the skin, even during the stage of deepest depression.

Acute death after reinjection does not occur as frequently as in the guinea pig, but nevertheless it is often obtained, provided that the sensitization has been produced with fairly massive doses (10 c.c. horse serum, for example), that the reinjection is not given before at least four weeks have passed and that the reinjection dose is 20 c.c. (see Fig. 7, page 120).

Man.—Whether true anaphylactic phenomena, in the sense of an antibody-antigen reaction, occur in the human being is the subject of some discussion at present. Coca, for example, discards serum disease, tuberculin sensitiveness, hay fever, food and drug idiosyncrasies, from the class of true anaphylactic reactions, and it must be admitted that his arrangement of the available facts seems to warrant this drastic action. Both Doerr and Wells have recently critically reviewed Coca's contribution without manifesting much sympathy but also without rendering Coca's position untenable. Many more facts are needed before a definite decision can be reached in this matter.

The human subject shows well-marked reactions, which are chiefly exhibited in the symptom-complex called serum disease by von Pirquet and Schick. In this group there are remarkable disturbances characterized by their occurrence after injection of some therapeutic serum which is usually obtained from the horse. These manifestations are general swelling of the lymph glands, skin eruptions of apparently inexhaustible variety, remittent fever, edema of the face and later of the dependent parts of the body, severe pains in the metacarpophalangeal, wrist, and knee joints without objective changes, and leukopenia. The time of onset or period of incubation of serum disease varies with the number of the injection; in reinjected individuals the period is much shorter than in those receiving the therapeutic serum for the first time. The percentage of incidence of the disease varies definitely with the quantity of the serum injected. A more detailed description of this interesting complex will be given later.

Serum disease is, however, not the only group of pathological changes evoked by foreign serum in sensitized man. Severe effects which threatened life, and even deaths, have been reported after the therapeutic injection of sera. The symptoms described indicate a sudden and remarkably severe effect upon the respiratory and cardiovascular systems, effects which especially characterize the anaphylactic reaction in the guinea pig, rabbit, and dog. Reactions of this character have been obtained in man with small doses of serum, not more than 1 c.c. in certain cases, and moreover after subcutaneous injection where absorption is necessarily slow.

Other Animals.—Though all the fundamental information we possess about anaphylaxis has been gained from the study of the animals mentioned, the reaction has been sought for in many other species. The results, however, do not yet warrant detailed consideration because little was accomplished beyond the demonstration that anaphylaxis occurs. The establishment of this fact is, of course, important, but otherwise the experimental yield was small. This result is perhaps due to the attitude of the investigators; most of them sought apparently only for those functional and anatomical changes which became obvious after they had once been pointed out.

Such a viewpoint, however, is not one which will increase our knowledge of the fundamental alterations which a new disease produces, for these alterations may differ considerably in the different species of animal due to their adaptation to special needs, although their systems of organs are qualitatively alike. A change which is profound, and even fatal, in one species may only be indicated in another and, indeed, might escape detection. For this reason it is necessary to study each species for itself, and while the investigator should be alert to note resemblances of reaction in the various species, he should be still more alert to discover new types of reaction. Comparative investigation of this character would give a rounded picture of the effects which the same process may induce. This is of special importance because man seems to have the capacity of reacting in many different ways to protein intoxication, and at least some of these human forms of reaction seem very similar, and may even be identical with those observable in various animals. As it is a priori probable that all the reactions occurring in man will show their analogue, if not homologue, in one or the other of the lower animals, the scientific and practical value of a comparative study of the phenomena in question is apparent, for a rigid experimental investigation, devised to answer specific questions, obviously cannot be carried out in man.

Experimental Analysis of the Anaphylactic Reaction

The anaphylactic reaction expresses itself by a primary or secondary disturbance in the function of numerous organs, and some of these disturbances may be more or less obvious on mere inspection. A closer insight into their mechanism, however, has only been obtained after the anaphylactic complex was analyzed from the viewpoint of modern experimental medicine, that is, when the ordinary procedures of physiology, pharmacology, and chemistry were brought to bear upon the problem.

It must be emphasized again that the anaphylactic alterations are the same, no matter what foreign soluble protein is used to produce them. In the following pages an experimental analysis of the anaphylactic symptom picture in the guinea pig, rabbit, dog, and man will be given. What the main symptoms are has already been indicated briefly.

Respiratory System.—Anaphylactic changes in the respiration are shown by the guinea pig in an exquisite fashion when the protein is reinjected intravenously, and mere inspection suffices to reveal them. The character of this involvement was not, however, realized until Auer and Lewis demonstrated that acute death in the anaphylactic guinea pig was due primarily to an asphyxia brought on by a swiftly developing stenosis of the bronchioles, and that this stenosis exhibited itself by a striking macroscopic alteration of the lung which could serve with proper precautions as an easy index for the anaphylactic reaction in guinea pigs. Evidence for these facts was brought out in a variety of ways. The guinea pig was allowed to breathe from an air container connected with a Marey tambour, which not only registered roughly quantitatively how much air entered and left the air receptacle at each inspiration and expiration, but also showed whether the air entered or left the lung promptly or slowly. At the same time the intrapleural pressure was recorded by means of a Meltzer pleural cannula. About half a minute after injection of the foreign protein into sensitized guinea pigs prepared in this manner it was noted that each inspiration and expiration recorded by the tambour in connection with the air receptacle showed a marked decrease in amplitude, and was of longer duration than before, as was indicated by the sloping course of the lever during its inspiratory descent and expiratory ascent. The intrapleural pressure changes corresponding to these respirations were greater than normal, showing that the animal was experiencing difficulty in getting air into and out of the lungs. After a few seconds the records showed that no air was entering or leaving the air receptacle, although the *intrapleural* pressure changes (due to the action of the respiratory muscles) were enormous. The action of the respiratory muscles was apparently unimpaired at this stage, and yet their tremendous efforts were entirely unavailing to cause any air to enter or leave the lungs; even the violent convulsions which now appeared had no effect upon the volume of the lungs, for the lever of the tambour connected with the air vessel and pulmonary air passages traced a straight line which was near the inspiratory level of the tracing. This experiment showed clearly that the nervous and voluntary muscular mechanism of respiration showed little, if any impairment, while the lungs were apparently the seat of some profound change which prevented the entrance and exit of air.

Experiments were then carried out with guinea pigs which had been curarized, whose vagi had been cut, or whose spinal cord, medulla, and basal brain had been destroyed by pithing. Artificial respiration was, of course, necessary under these conditions to maintain life. When the intrapleural pressure of such animals was recorded the tracings gave valuable information. Shortly after injection of the toxic dose the tracing, which records the fluctuations of intrapleural pressure brought on by the constant volumes of air forced rhythmically into the lungs through the trachea, shows remarkable changes. Immediately after the injection the excursions of the lever decrease moderately in amplitude, then they increase in amplitude, and finally they decrease rapidly to such a degree that the lever does not record any respiratory fluctuations at all, though the machine delivers the air at the same rate, pressure, and volume as before. The lever comes to rest, as far as respiratory oscillations are concerned, at various points between the expiratory and inspiratory levels of the tracing, never, however, in a typical experiment at the expiratory level. The lever records now only the volume changes of the heart (see Fig. 1). Similar tracings were obtained when a lobe of a sensitized guinea pig's lung was placed in an oncometer and its volumetric oscillations with artificial respiration recorded before, during and after an injection of the toxic dose of protein.

These experiments show definitely and unmistakably that the second injection causes by peripheral action in the lung (the central nervous system being excluded by pithing) a stenosis in the air passages, which becomes so extreme that the respiration machine cannot force in air; the complete stenosis being preceded by a period of increased ease of entry of the air; and this, in turn, being preceded by a period of slightly decreased ease of entry, shown by fluctuations in the amplitude of the lever which records the volume of the lungs or the intrapleural pressure. The records also show that the final volume of the lungs must be greater than the normal expiratory volume of the organ, for the lever comes to rest at a higher point than the expiratory level. Figure 1 illustrates these changes.

A condition of such extreme stenosis of the air passages that the most violent inspiratory and expiratory efforts of the animal, or the blast of a respiration machine, cause no change in the volume of the lung must obvi-

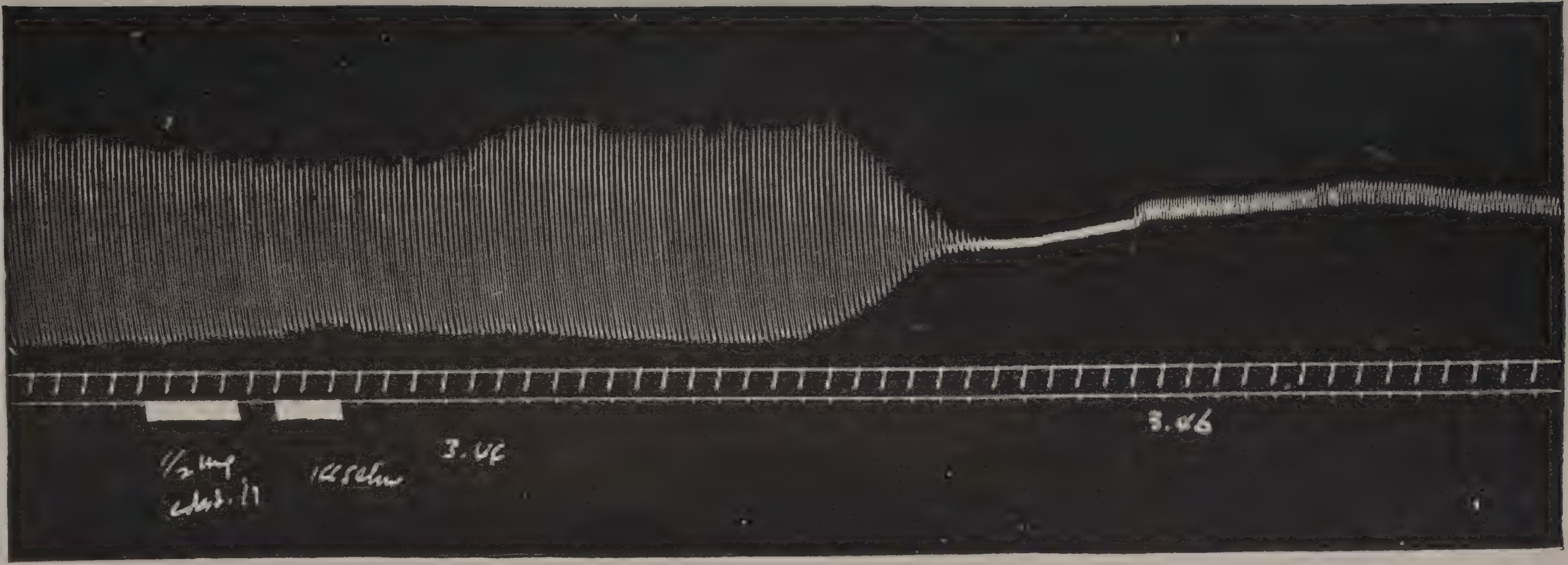

FIG. 1.—VOLUME CHANGES OF THE LUNG IN A GUINEA PIG DURING ACUTE ANAPHYLACTIC REACTION. The tracing was obtained from a pithed guinea pig by means of a pleural cannula connected with a Marey tambour. Upstroke of the recording lever means inflation; downstroke, collapse of the lung (artificial respiration throughout the experiment).

The animal was sensitized by 3 mg. of edestin dissolved in 1/20 NaOH injected subcutaneously. After about six weeks 0.5 mg. of edestin in 1/20 NaOH was injected into a jugular vein (first broad white band in the tracing; the second white band below the time line, which records 4 second intervals, shows the injection of 1 c.c. saline solution to wash out the cannula).

Note the initial decrease in the amplitudes after the injection of serum (bronchoconstrictor effect); then the increased amplitudes (bronchodilatation) and finally the abrupt abolition of all pulmonary oscillations, although the artificial respiration machine delivers the same amount of air as before (extreme bronchoconstrictor effect). Now only the volume changes of the heart are recorded; note the abrupt changes in heart rate: two stages of cardiac block are recorded.

ously bring about asphyxia. Hardly any other proof is necessary, but additional evidence is easily brought forward. If the blood-pressure is recorded in an anaphylactic guinea pig it will be noticed that within one minute after the reinjection the blood in the cannula turns very dark, even black; the mucous membrane of the mouth becomes bluish, the pupils dilate widely, and violent convulsions appear. If a sample of blood is now taken from an artery it looks almost black, but becomes bright red when diluted with a little salt solution and shaken a few times. Though no gas analyses have been made of the blood, it seems quite certain that carbon dioxid is present in large amount. Cardiac failure is not the cause of this asphyxia, because the heart keeps on beating regularly and powerfully for many minutes after all respiration has definitely ceased. If on autopsy the root vessels of the heart are compressed by a dissecting forceps, the organ excised, and the forceps released, the systole of the heart drives the black blood in the left ventricle several inches into the air. Failure or weakness of the cardiac pump thus cannot play an important rôle in the production of this high grade of asphyxia.

It was stated before that the evidence indicated that the volume of the lung after acute anaphylactic death is greater than that of the lung at the time of a normal expiration. The autopsy of any guinea pig which dies acutely (three to ten minutes) from the reinjection gives full support to this inference and furnishes the anatomical evidence for the functional respiratory alterations which have been described. Auer and Lewis describe the lung picture as follows: On opening the chest the lungs present a striking sight; the lungs do not collapse, as normal lungs do when the thoracic cavity is opened, but remain almost fully distended. They look pale bluish-pink, and apparently form a cast of the thoracic cavity; even when excised *in toto* there is practically no collapse, and the posterior surfaces of the lung often clearly show the markings of the ribs. The excised lungs are light, soft, and spongy, and float on water like a cork. Pieces of lung tissue cut off do not collapse, but remain distended; the surface of the cuts is usually dry, and on pressure a good amount of air can be expressed. Occasionally this pressure reveals some small foci of white foam, as if there were beginning pulmonary edema; occasionally small hemorrhages were seen on the surface of the lungs. The trachea and bronchi usually were dry, but often showed a marked congestion of the mucosa.

Figure 2 illustrates this remarkable lung condition, which was first noted, but only casually described, by Gay and Southard, although these authors definitely state that they were "inclined to regard this emphysema as the effective cause of death in the quickly fatal cases."

The causation of this interesting anatomical change in the lung was attributed by Gay and Southard to an emphysema produced by a diaphragmatic spasm, which is secondary to a stimulation of the medullary and phrenic centers of respiration. Auer and Lewis disproved this theory by showing that the typical lung picture is promptly obtained in guinea pigs which have been curarized, or whose central nervous system has been destroyed. These authors advanced the view which has been generally accepted that the anaphylactic lung in the guinea pig is produced by a tetanic contraction of the muscles of the finer bronchioles. Their reasons were briefly as follows: the fluctuations in volume which the anaphylactic lung shows during artificial respiration; their final disappearance, leaving the lung in a fixed inspiratory position even when excised; the absence of collapse of small pieces when cut off; the rich content in air; moreover, the fact that atropin can reëstablish the rhythmic expansion and collapse of

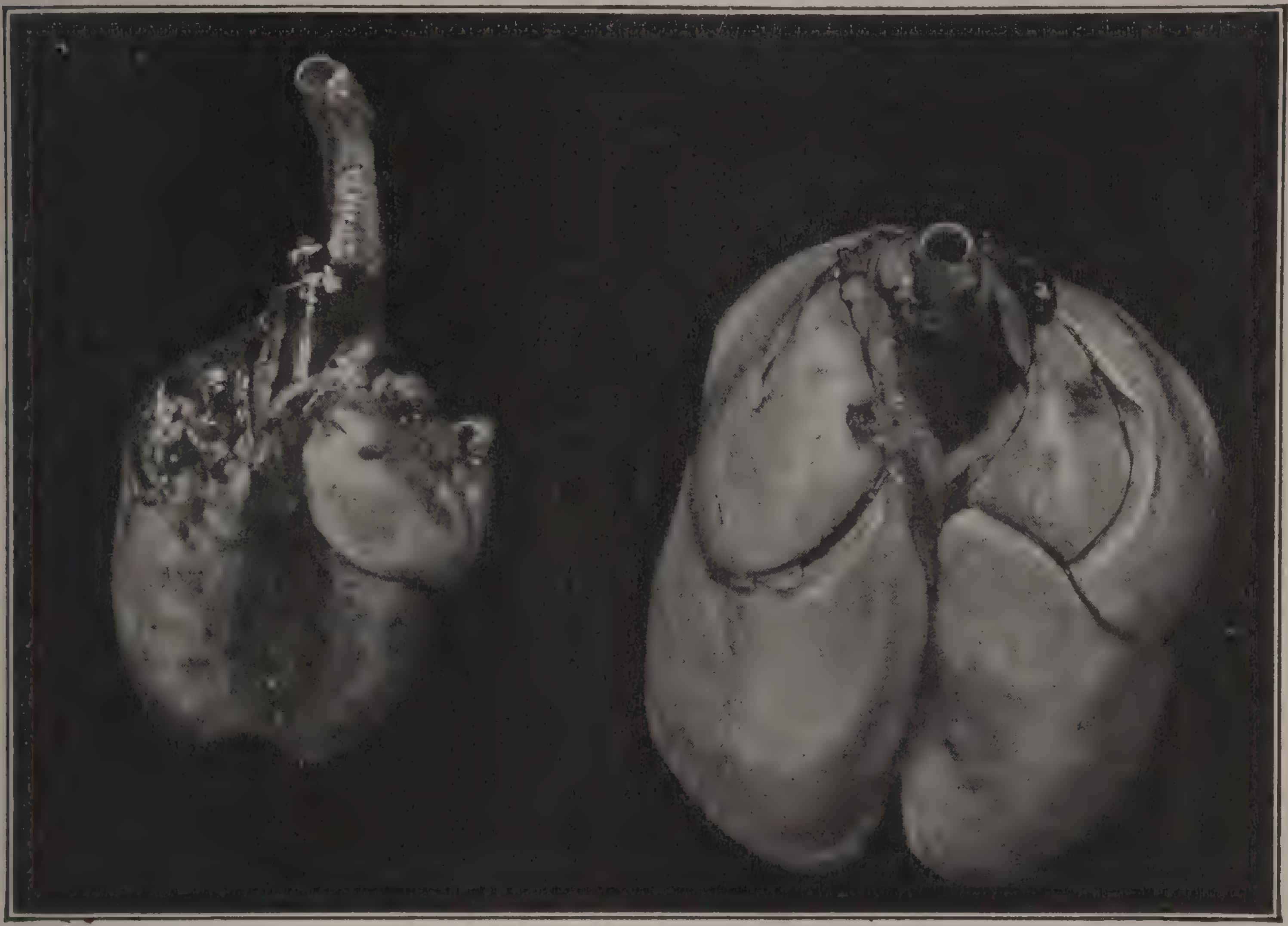

Fig. 2.—Anaphylactic Lung after Degeneration of the Right Vagus in Guinea Pigs, with and without Atropin; Posterior View. The figure on the left shows a practically normal collapsed lung. The figure on the right illustrates the typical anaphylactic lung. Both guinea pigs were sensitized by subcutaneous injection of 1 c.c. horse serum. After fifty-five days the right vagus of each was resected in the neck. After sixty-eight days from the date of sensitization both received 0.3 c.c. of a 10 per cent solution of heated horse serum intravenously. One animal was previously given 3 mg. of atropin sulphate subcutaneously. The atropin animal exhibited but slight symptoms of anaphylaxis and was killed later by severing the medulla; the lungs collapsed in a normal manner on opening the chest except the right upper lobe. The second guinea pig, however, died within five minutes of the injection of serum and its lungs showed the typical anaphylactic fixation in a full, inspiratory position. The pictures also show that the denervation of one side of the lung exerts no effect on the anaphylactic reaction, or upon the action of atropin.

a typical, immobile, anaphylactic lung; all these facts indicated that the muscles of the finer bronchioles were at fault, for previous work had established that these structures profoundly affected the function of the lung. It was well known that stimulation of the peripheral vagus nerve caused contraction of the bronchioles and produced stenosis effects in the lung (Einthoven, Dixon and Brodie), and these effects were apparently identical with those recorded in the anaphylactic guinea pig; it was also established that blood vascular changes due to this stimulation of the vagi would not account for the lung changes (Dixon and Brodie). Furthermore, since Dreser and others showed that atropin abolished the bronchomotor effect of vagus stimulation, it seemed legitimate to attribute the anaphylactic lung changes in the guinea pig to a tetanic contraction of the muscles of the finer bronchioles which effectively occluded their lumen so that the contained air was imprisoned and the animal necessarily succumbed to an asphyxia.

This mechanism easily explains how the distended inspiratory state of the lungs is produced and maintained. As the bronchial muscles gradually begin to contract the lungs fail to collapse fully during expiration because the air now leaves with greater difficulty, due to the narrowing air passages. Some air therefore remains in the lungs when the next inspiration occurs. This incoming air meets the same resistance, but nevertheless more air enters the alveoli than leaves them, because each inspiration utilizes the entire available passageway, for the increased negative pressure in the thorax tends toward an opening of the bronchioles. Expiration, on the other hand, and especially active expiration, tends toward narrowing still further the already narrowed tubes by increasing the pressure resting on the outside of these tubes, for the intrathoracic pressure becomes positive during active expiration. Therefore, in spite of the fact that the expiratory efforts of the animal are more powerful than the inspiratory efforts, less air is expelled than taken in, and the lungs must become sooner or later maximally distended. Moreover, this deficient alveolar ventilation leads to an accumulation of CO_2, and this gas has been shown by Einthoven and by Dixon and Brodie to produce a tonic constriction of the bronchial muscles. This increases the stenosis, and consequently the asphyxia, still more, until no air enters or leaves the lung and the animal succumbs. If the lungs are now excised they will be found in a state of maximal inspiration, which is maintained for hours (see Fig. 2).

A beautiful picture of the whole process may be easily obtained by observing the effect of the reinjection in a pithed guinea pig whose chest has been split transversely. After injection of the toxic dose one may see that the artificial respiration at first produces a greater expansion and collapse of the lungs due to a relaxation of the bronchomotor muscles; very shortly after this the lungs do not collapse fully during expiration, and with each succeeding blast of air the expiratory collapse of the lungs becomes less and the distention more, until after a few minutes the artificial respiration produces no further increase and the expiratory pause no decrease in volume. The lungs are fixed in an immobile, inspiratory position, which is not altered when the organ is excised.

The experimental facts brought forward by Auer and Lewis were soon corroborated in general by a number of observers, especially Anderson and Schultz, and Biedl and Kraus, and at present no one doubts that acute anaphylactic death in the guinea pig is caused by an asphyxia which is brought on by the development of a stenosis in the pulmonary air passages of the animal. The only exception is perhaps Richet, who is unwilling to accept the interpretation that a tetanic contraction of the bronchioles causes the asphyxia to which the guinea pig succumbs, because (1) this is not the cause of death in dogs, and it is inconceivable to Richet that the anaphylactic reaction in the guinea pig and dog is different; (2) artificial respiration does not prevent death; (3) it has not been proved that the blood is asphyctic. The reader will notice that most of the objections urged by Richet have already been partly answered. Auer and Lewis and Biedl and Kraus showed definitely in graphic records (see Fig. 1) that artificial respiration does not save the life of the guinea pig for the simple reason that the air cannot enter the lung because of the stenosis in the air passages; even a pressure of such degree that enough air was discharged per blast to satisfy the needs of an adult dog was insufficient to overcome the stenosis (Biedl and Kraus). The same thing is true when the anaphylactic animal breathes spontaneously: after a certain time no air enters or leaves the alveoli; it therefore would be perfectly useless to place animals in an atmosphere of oxygen as Richet suggests, for none of it could enter the alveoli after the anaphylactic reaction was fully under way. The other objection that it is inconceivable for anaphylaxis to be different in the different animals will answer itself in the section dealing with the analysis of the symptoms in the different animals. It may not be amiss in passing to point out that an attitude which a priori demands an identity of reaction to the same causative agents in different animal species necessarily leads to erroneous conclusions.

By further experimentation upon guinea pig's lungs Auer demonstrated that the typical anaphylactic lung picture could be obtained after the bronchial muscles of one side of the lung had been deprived of their motor innervation by section of the corresponding vagus in the neck, for each vagus sends postganglionic bronchomotor fibers largely if not entirely to its ipselateral lung in the guinea pig (Auer) as well as in cat, dog and rabbit (Dixon and Brodie). In a number of series of animals one vagus was resected either before or after sensitization had been established; the reinjection was given after various time intervals. The result showed no definite difference between the two halves of the anaphylactic lung (see Fig. 2). As thirty-three days passed in one series between vagus section and the injection of the sensitizing dose, and the second or toxic dose was injected fourteen days later, and as the resultant lungs did not differ from those obtained in guinea pigs with intact vagi, it is legitimate to assume that the nerve and nerve endings were degenerated, and that the denervated muscle itself responded to the sensitizing and the intoxicating doses. Auer obtained no evidence that the vagus bronchomotor endings played a rôle in the production of the anaphylactic reaction, but does not deny this possibility.

The anatomy and histology of the anaphylactic guinea pig's lung were extensively studied. Schultz and Jordan, in a valuable contribution, proved among other facts that the stenosis of the pulmonary air passages which causes death is localized in the secondary and tertiary bronchi. The tetanic contraction of the muscle coat folds the mucous membrane of this area into a plug which occludes the lumen, and thus brings about asphyxia. The air passages below the level of the secondary and tertiary bronchi were found open, even distended. Schultz and Jordan's studies, made upon stained sections and complete dissections of the bronchial tree of normal and anaphylactic lungs, do not entirely explain the distention of the anaphylactic lung, for small pieces of the lung cut from the periphery of the lobes do not collapse. It is possible that this is due to an increase in the rigidity of the tissue elements. The same authors also note the presence of edema near the bronchial tree. This edema, however, is only rarely extensive, and in the vast majority of experiments with non-toxic sera the lungs show only traces of edema (Biedl and Kraus). If, however, primarily toxic sera are employed, Karsner demonstrated that the guinea pig's lungs show marked evidences of conglutination of the red corpuscles, hemolysis, hemorrhage, and edema.

The Lungs in Subacute Anaphylaxis.—The macroscopical change in the lungs of the guinea pig which succumbs to acute anaphylaxis are practically not observable when the injected animal dies after the lapse of one-half to several hours. In these delayed cases the lungs usually collapse fairly completely when the thorax is opened. The degree of the collapse observed seems to depend upon the severity of the symptoms and the speed with which death ensues; the sooner death occurs the greater is the distention of the lungs. If guinea pigs are killed shortly after the main symptoms of a sublethal intravenous injection have passed off, the lungs always fail to collapse as completely as in a normal animal; one or the other lobe of the lungs, if not all, will always show distention. This demonstrates that the same qualitative change took place in the lungs, though it was not great enough to produce acute exitus. The cause of death in those animals which die subacutely has not yet been established. It is very probable that a number of factors together produce this result, for in these delayed cases extensive hemorrhages are often found in the gastro-intestinal canal, diaphragm, lungs, heart (Gay and Southard); the vessels of the splanchnic area are dilated, indicating a low blood-pressure, and the initial asphyxia which is maintained later at a lower level probably also aids in bringing about death.

Lung Changes in Other Animals.—As acute anaphylactic death caused such a pronounced anatomical and functional change in the lung of the guinea pig, it was perhaps natural to expect that a similar change would be found in other species of animals. The inference did not prove true, however, at least as far as the dog and rabbit are concerned, and this difference at first produced some confusion among investigators who postulated an identity of the anaphylactic reaction in all animals. In rabbits, for example, which have succumbed acutely to the reinjection the lungs collapse well, but not completely; they look mottled, and occasionally hemorrhages are seen on the surfaces. On closer inspection numerous areas of emphysema are usually visible on the surfaces and borders; the large distended air sacs composing these areas of emphysema are easily visible to the unaided eye. A cut surface may show small areas of fine foam on pressure, as if there were beginning pulmonary edema. The trachea, as in the guinea pig also, looks bluish and the mucosa is strongly congested. The congestion extends into the pulmonary bronchi (Auer). Scott states that the lungs of rabbits retract normally and are rather pale; microscopically he describes and pictures a thickening of the interalveolar septa; the capillaries were compressed and the blood-corpuscles seemed peculiarly adherent to the walls. Scott never saw a general edema, though some alveoli contained a little serous exudate, but the lung condition suggested a very early stage of acute edema to him. Doerr states that he occasionally observed rabbit lungs which bore some resemblance to those observed in the guinea pig.

In the non-fatal anaphylactic reaction of the dog the lung differs but little, if at all, from that of a normal dog; the lungs collapse well on opening the chest, and show smooth surfaces and borders. There is no indication of any local emphysema such as the rabbit shows, nor are any hemorrhages to be observed on the lung surfaces. There is, however, a functional disturbance, the spasmodic expirations during the stage of excitation which Biedl and Kraus are inclined to interpret as due to a stimulation of the bronchial muscles.

In dogs which succumb acutely the lungs do not collapse completely as a rule, but often remain more or less distended on excision like the anaphylactic lungs of a guinea pig. They are large, pale, doughy, and pieces which are cut off remain distended and are full of air. There is no pulmonary edema, nor are hemorrhages detectable on the surfaces of the lungs. The lungs of the dog which furnished the tracing for Figure 7 were of this character.

In man marked respiratory disturbances are occasionally noted, which may be identical in their causation with those observable in the guinea pig. These and other symptoms which have been described will be considered together in another section of this chapter.

Cardiac System—*Anatomical Changes.*—The heart shows a number of anatomical and functional changes during the anaphylactic reaction which have not been extensively studied so far. Gay and Southard, in their valuable histological studies of the anaphylactic guinea pig, were the first to describe cardiac hemorrhages. The hemorrhages are found chiefly on the ventricular surfaces, especially near the apex; the auricles show but few small punctate hemorrhages, which are never extensive, and indeed may be absent entirely, at least on macroscopical examination.

Both in the guinea pig and the rabbit the production of these cardiac hemorrhages may be directly observed when the thorax is split and the anesthetized animal kept alive by means of artificial respiration. Shortly after the injection of the toxic dose of protein the ventricle, right or left, may show suddenly a dark red spot which often rapidly grows and forms a moderately raised mass during systole of the heart. The hemorrhages may be fairly numerous and discrete; at times, however, they are quite extensive and involve a large part of the ventricular portion of the heart (Auer).

These hemorrhages, visible from the pericardial surface of the heart, are especially pronounced in the guinea pig, and are not obtained to the same degree in rabbits. In the cat subpericardial hemorrhages have been observed by Schultz. In dogs hemorrhages visible on the pericardial surface have not been described at all as far as the writer is aware; nevertheless in this animal also gross cardiac hemorrhages occur, but they have not been observed before because comparatively few dogs succumb acutely. The hearts of such dogs often show marked, radially arranged hemorrhages beneath the endocardium, especially on the septal surface of the left ventricle. These hemorrhages in the interior surface of the left ventricle almost invariably involve the left branch of the His bundle (the left branch of Tawara) which forms two main divisions. These branches often show blood-red sections, which may be extensive, where a hemorrhage has occurred into them. In addition there are also hemorrhages into the papillary muscles. The left ventricular cavity shows more extensive hemorrhages than the right. The auricles show but few, if any, hemorrhages, and those are only visible when the auricles are split open (Robinson and Auer).

Subendocardial hemorrhages of the kind described for the dog are frequently observable in the rabbit and the guinea pig (Auer).

These hemorrhages are not to be explained as the result of violent convulsions during which the general systemic blood-pressure is increased, because the hemorrhages are also obtained in curarized or anesthetized guinea pigs, rabbits, and dogs, where the animal remains perfectly quiet. The systemic blood-pressure, moreover, seems to play a subsidiary rôle, because, in the dog, the blood-pressure is low—40 mm. approximately —within less than a minute after the reinjection, and yet the endocardial hemorrhages in this animal may be just as extensive as in the rabbit and guinea pig, where the blood-pressure curve in the fatal cases shows an initial rise and subsequent slow fall. These hemorrhages seem rather to be the result of local constrictions which appear in the veins and venules (see below). These constrictions of the venules in the heart must necessarily impede their emptying which occurs during systole, and the blood must be dammed back behind the stenoses. When this occurs near the surface of the heart, where the support of the venules and capillaries is least, ruptures of the wall and consequent hemorrhages take place when the heart contracts. It is possible that a direct injury of the capillary endothelium also occurs in the anaphylactic reaction, such as Heubner postulates for the explanation of capillary hemorrhages after the intravenous injection of widely different chemical substances (salts of the heavy metals, tartar emetic, emetin).

Hemorrhages are not the only gross anatomical changes which are detectable in the anaphylactic heart, though they form the only one described so far for both the guinea pig and the dog. In the rabbit which has succumbed acutely the right ventricle often shows a gray color, decreased translucency, and a peculiar stiffness of the wall becomes apparent when the right ventricle is slit open for further examination. The right ventricular wall feels firmer than normal on pressure, and this increased firmness is strikingly shown by the resistance of the endocardial surface to the finger nail. If the endocardial surface of the right ventricular wall (not the septal surface) is scraped, the muscle tissue, especially the muscle trabeculæ of the upper third of the ventricle, resists the finger nail much as if it were connective tissue. The papillary muscles of the right ventricle show a similar resistance, though not as great as that of the wall. The left ventricle, however, shows no indication of this change, and the finger nail easily scrapes off muscle tissue. Similar changes of the cardiac muscle may be produced by intravenous injections of lethal doses of digitalis preparations. Auer interprets these alterations as an intravital rigor.

Functional Changes.—The anatomical changes briefly described in the preceding paragraph would naturally lead one to expect some functional alterations as the result of these gross anatomical changes, and such functional alterations are easily detectable.

If the heart of an anaphylactic guinea pig is examined immediately after respiration has ceased, it will be found contracting vigorously, but the ventricles beat slowly and do not respond to each auricular systole; in other words, there is a state of partial auriculoventricular dissociation or block, and the ventricles respond only to every second, third, or even fourth auricular contraction. The finer degrees of dissociation where a ventricular beat drops out after a varying number of complete cardiac cycles obviously cannot be detected by mere inspection. Cardiac block during an anaphylactic reaction in a guinea pig was first described by Auer and Lewis; it may occur within thirty seconds after the lung has been completely immobilized by the foreign protein, as shown in Figure 1 accompanying this article. The same figure also shows a second abrupt change in the cardiac rate occurring about one-half minute after the first one. The strength of the cardiac contraction does not seem much affected, for the ventricles are able to propel the blood several inches into the air when the aorta is cut immediately after the heart has shown some changes in rhythm. According to Auer and Lewis, the block is due to an asphyxia which acts directly on the heart itself, for these alterations in rhythm are just as easily obtained in a pithed animal as in a normal one. While this interpretation is in accord with the action of asphyxia in decapitated atropinized cats (Sherrington, Lewis and Mathison), nevertheless it seems possible that systemic asphyxia is not the only cause of this cardiac block in the guinea pig because, in the dog and rabbit, block occurs under conditions where systemic asphyxia does not exist. To decide this question the experiment must be carried out in the excised heart, for only in this way can systemic asphyxia be excluded as a causative factor (see page 118). It is probable that the heart plays only a secondary part in acute anaphylaxis in the guinea pig, for death in this condition is caused by a general asphyxia due to bronchiolar stenosis.

In the rabbit cardiac disturbances play a prominent rôle, and it will be shown that cardiac failure is one of the causes of death in the acutely fatal cases. When the heart is examined in situ immediately after respiration has ceased, which usually occurs two to five minutes after reinjection in well-sensitized animals, this organ will be found in diastole, the ventricles contracting feebly or not at all, while the auricles beat fairly strongly and at a more rapid rate than the ventricles. Mechanical or faradic stimulation of the ventricles has little or no effect. This loss of contractility of the heart occurs just as swiftly when the rabbit is tested under artificial respiration, when the vagi are cut and after the entire central nervous system has been destroyed (Auer). In some experiments the heart may cease to beat abruptly at a time when the blood-pressure is excellent and when the curve shows no abnormalities except that the respiratory waves are absent, even though artificial respiration has been maintained throughout.

While all the evidence so far described seems to indicate that the heart is the primary seat of these changes, further experiments have shown that some of the cardiac changes may be in reality of secondary origin. Coca has recently presented physiological evidence that the pulmonary arterial circuit was strongly stenosed in rabbits which had suffered an anaphylactic reaction. Thus a pressure of 10 cm. saline solution produced a good flow through the pulmonary artery and veins in normal rabbit, while a pressure of 70 to 90 cm. caused but a slight flow in rabbits succumbing to an anaphylactic reaction. Since the same stenosis was obtained with dissolved protein (laked corpuscles) as with corpuscles, Coca infers that the pulmonary arterioles are contracted, though he could not demonstrate this anatomically. This observation of Coca will explain the sudden drop in blood-pressure observed in the rabbit, and, as Coca remarks, it may also explain why the right ventricle of a rabbit succumbing acutely should show rigorlike changes which are not present to the same degree in the left ventricle. The development of a stenosis in the pulmonary arterial system, however, cannot be utilized to explain all the cardiac changes which have been observed in the anaphylactic heart: for example, the speedy loss of irritability in both ventricles of the rabbit, the development of cardiac hemorrhages in the rabbit and finally the experiment on the excised heart by Cesaris-Demel and by Launoy.

Though these functional disturbances, together with the anatomical changes, show clearly that the heart is damaged in the acutely fatal cases in rabbits, the cardiac changes leading up to the fatal issue had not been investigated with care. For this purpose the electrocardiograph is essential because it permits a careful study of every heart beat from the beginning to the end of an experiment. In an investigation of the anaphylactic rabbit, by means of the electrocardiograph, carried out by Auer and Robinson, a variety of alterations in the character and sequence of the heart beat was observed. These authors describe abnormalities which occurred in a great majority of their experiments (twenty-two out of twenty-four). The changes noted, irrespective of whether the vagi were cut or not or whether the issue was death, were (1) alterations in the P wave, which disappeared at times or appeared very close to the R wave, so that the ventricular cycle, the R-T complex, could not possibly be due to the auricular (P wave) impulse; (2) abnormal R waves, the downstroke being slow; (3) the development of prominent S waves; (4) changes in the T wave which disappeared, became negative, or increased in size. These changes in auricular and ventricular activities often occurred without any alteration in the conduction time between auricles and ventricles.

Changes in the conduction time between auricle and ventricle (P-R interval) were observed that led to partial or even complete dissociation. This block was only obtained when rabbits with intact vagi succumbed acutely. The dissociations were especially interesting because of a rhythmic appearance and disappearance, which took place two and even three times, the periods between the dissociation showing a normal sequential beat, though the conduction time was prolonged. Moreover, the electrocardiograms obtained for a short time early in the experiment occasionally showed alterations which seemed identical with those obtained when respiration had ceased, and these changes were of a type which

Robinson describes as characteristic of a dying heart: the T waves are sharp, prominent, and occur close to the R waves; the R waves themselves are rather broad, due to a slow downstroke which does not fully reach the base line.

Another interesting alteration which the same authors observed was an abnormal relation between the P and R waves. In seven experiments the conduction time between auricle and ventricle (P-R interval) was temporarily shortened. For example, in an experiment the normal P-R interval was 0.08 second, while two minutes after the injection it had diminished to 0.033 second. This shortening of the interval, like the block, was of temporary duration and, again like the block, sometimes appeared, then disappeared, and again reappeared. Similar changes have been obtained by Rothberger and Winterberg after stimulation of the left accelerator nerve in the dog. Rothberger and Winterberg believe that the power of stimulus formation of the junctional tissue has been raised by stimulation of the accelerator nerve, so that this region becomes the cardiac pace maker. The same change probably also occurs in the anaphylactic heart, and the point of origin of the heart beat shifts repeatedly from the sinus region to the junctional tissue between auricles and ventricles, which explains the shortening of the P-R interval and the fact that the auricles and ventricles contract almost simultaneously. It is possible that accelerator stimulation also plays a rôle in these changes of the anaphylactic heart, for the cardiac rate usually shows an outspoken augmentation in rate. Nevertheless, the approximation of P and R waves has been observed without any acceleration (see Auer and Robinson, Plate 35). This abnormal relationship between the P and R waves occurred in rabbits with vagi intact or sectioned, and in fatal as well as in non-fatal cases.

The time of onset of the cardiac changes varied in the different series of rabbits and occurred soonest in the acutely fatal cases where alterations were often observable before the injection, which usually lasted about one minute, was finished. This was especially true of the animals with intact vagi, while those with sectioned vagi responded within three-quarters to two and a half minutes after the beginning of the injection. No such difference was, however, noted in the non-fatal cases; there the alterations appeared within one to five minutes after the beginning of the injection, irrespective of whether the vagi were cut or intact. No definite statement can therefore be made regarding the influence of the vagi on the onset of the cardiac symptoms.

The cardiac changes recorded by the electrocardiograph occurred in the fatal cases before respiration ceased, and therefore cannot be attributed to a general asphyxia. This inference is still further strengthened by the non-fatal experiments where the respiration was never embarrassed, although the electrocardiograms showed a variety of abnormalities.

The duration of these changes varied; in the fatal cases they appeared, lasted a short time, and disappeared, to appear again after a period of normal beats. This continued until the animal died. In the non-fatal cases with vagi intact the abnormalities lasted seven to twenty-one minutes; in the series with vagi cut the duration was shorter, only two and one-half to five minutes. This difference seems to indicate that some effect is exerted upon the vagus center during the anaphylactic reaction.

That the electrocardiographic abnormalities were really of anaphylactic origin Auer and Robinson demonstrated by failing to obtain them when the antigen (horse serum in this instance) was reinjected intravenously into sensitized animals after the effects of the first reinjection had passed off and when the animals were therefore antianaphylactic. Normal rabbits also failed to show the characteristic changes when injected with horse serum, but in one of these controls premature, ectopic beats developed. As these extrasystoles were also observed in a sensitized rabbit which had been again reinjected immediately after recovery from the first intoxicating dose, Auer and Robinson are inclined to regard these extrasystoles as probably not significant when they occur in the anaphylactic state.

Hecht and Wengraf also have examined young rabbits with the electrocardiograph during horse serum anaphylaxis. The main disturbance these authors observed were extrasystoles of the apical type; they also noted negative P waves, flattened or negative T waves, and the development of S waves. Disturbances of conduction or the development of block were not obtained by them.

Alterations in the rate of the heart beat appear most sharply, like most anaphylactic reactions, when the reinjection is given intravenously. If the blood-pressure of an anaphylactic rabbit is recorded by means of a membrane manometer, which gives a fairly accurate picture of the individual pressure pulse beats, the following alterations may be observed. Toward the end, or shortly after the reinjection, the heart slows moderately; this slowing lasts less than a minute and suddenly gives way to a very rapid small pulse. This rapid pulse may persist with a gradually sinking blood-pressure until the heart stops beating. As a rule, however, the rapid pulse rate is interrupted by short stretches of large, slow pulses. As the initial slowing of the rate is obtained just as well in rabbits with vagi cut as in those with vagi intact, the effect cannot be of central origin, but must be peripheral, and occurs perhaps in the vagus endings of the heart itself. The increase in rate which occurs later may possibly be due to a stimulation of the accelerator nerves; whether this stimulation is peripheral, acting on the accelerator cardiac endings, or whether the effect is exerted centrally in the medulla, cannot be decided with the evidence available at present. It has already been stated that this acceleration may have some relation to the approximation of P and R waves, which was noticed first by Rothberger and Winterberg.

The dog also shows cardiac derangements which are directly attributable to the anaphylactic reaction. That the heart is involved is already indicated by the fact that this organ shows a definite abnormal reduction in direct irritability when examined immediately after acute anaphylactic death. Moreover, the location of subendocardial hemorrhages in the conducting system, which have already been described, would also lead one to expect some functional expression for these anatomical changes. The ordinary methods, however, failed to detect any primary anaphylactic effect on the heart of dogs. Biedl and Kraus never observed any cardiac irregularity at any time during the reaction, and they emphasize the fact that a slowed and perhaps irregular activity of the heart is replaced by a remarkable regularity during the stage of low blood-pressure. Eisenbrey and Pearce tested the question experimentally and recorded the heart's activity by means of a Cushny myocardiograph. They found no evidence that the functional activity of the sensitized dog's heart was primarily affected by the injection of the toxic dose. Certain changes which occurred in the myocardiograph tracing after a low blood-pressure level had been reached were attributed by Eisenbrey and Pearce to an incomplete filling of the right heart; both the right auricle and right ventricle showed a marked decrease in size, and the right ventricular wall appeared flabby and collapsed during diastole, but contracted in rate, extent, and regularity just as it did before the injection.

Positive evidence that the heart of the anaphylactic dog may show irregularities was brought forward by Robinson and Auer. They examined the animals by means of the Edelmann large model electrocardiograph, and the electrodes were applied to the right front and the left hind leg (lead 2). These authors found that cardiac disturbances are much less frequent in the dog than in the rabbit, where the anaphylactic reaction almost invariably brought on some cardiac change. Out of twelve dogs only six exhibited well-marked pathological electrocardiograms, and these occurred whether the vagi were intact or sectioned at the time the intravenous reinjection was given. All of these animals showed disturbances of the conduction time (P-R interval). In five the P-R interval was lengthened, and in two animals this lengthening was so marked that partial auriculoventricular dissociation of varying degree took place. Figures 3 to 6 illustrate two stages of partial heart block obtained from one dog. In Figure 4 every eighth auricular impulse is blocked, and in Figure 5, a later stage, every fourth auricular impulse fails to produce a ventricular contraction. The conduction time varied between 0.12 and 0.28 second during the block, while normally it was 0.08 second.

In one animal with intact vagi the P-R interval was practically abolished and auricles and ventricles beat synchronously. This occurred with a blood-pressure of 30 mm. of mercury while the heart was beating 148 per minute. The P and R waves gradually separated, the P waves being negative at one stage, and thirteen minutes after the onset the electrocardiogram was normal, the P-R time was 0.10 second, the rate 167, and the blood-pressure 40 mm. This type of alteration has already been discussed in the paragraphs dealing with cardiac disturbances in the anaphylactic rabbit, where it occurs more frequently, and attention was there called to the similar changes which Rothberger and Winterberg obtained when the left accelerator nerve was stimulated in dogs. In the anaphy-

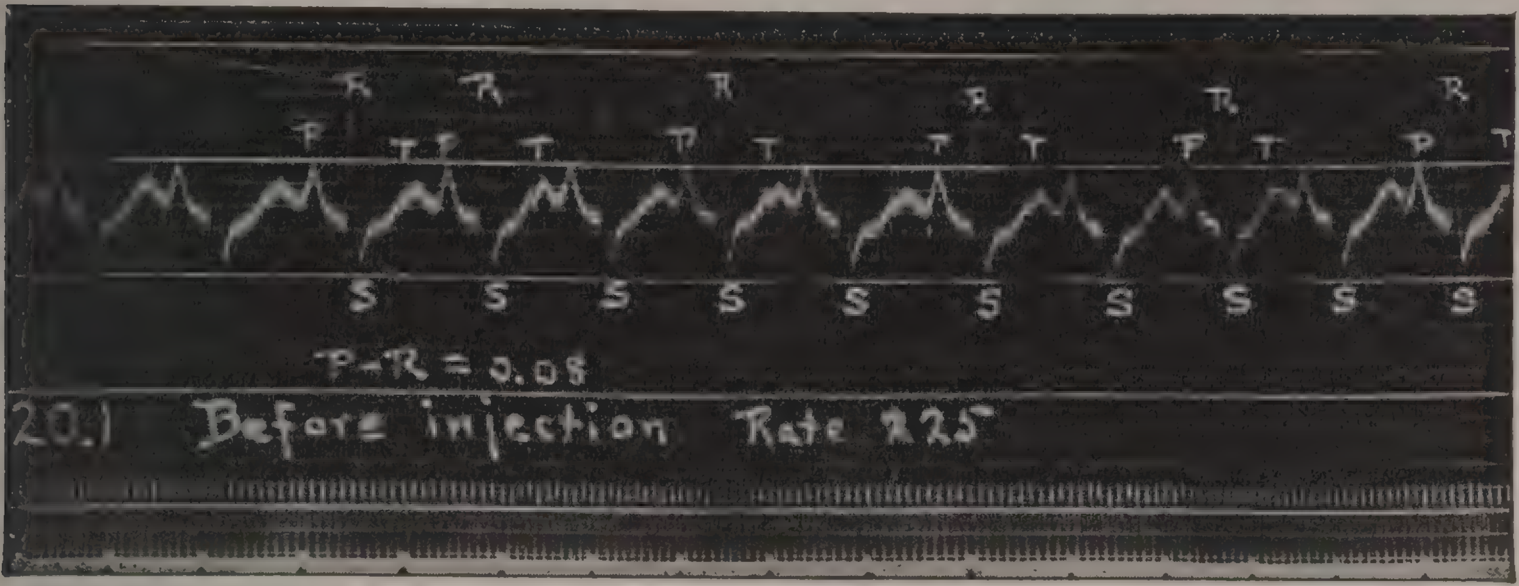

FIG. 3.—ELECTROCARDIOGRAM BEFORE INJECTION. Conduction time between auricles and ventricles, 0.08 second; rate, 225.

Figures 3 to 6 show partial auriculoventricular dissociation due to anaphylaxis. Male dog sensitized by the subcutaneous injection of 5 c.c. sterile horse serum into each flank. After sixty-one days etherized fully and electrocardiographic records taken with needle electrodes from the right front and left hind legs (lead 2). The string of the galvanometer was so adjusted that 1 millivolt gave an excursion of 1 cm. on the curve. The vagi were intact. The dog recovered fully and was lively on the next day. Electrocardiograms taken two days after the injection showed normal complexes.

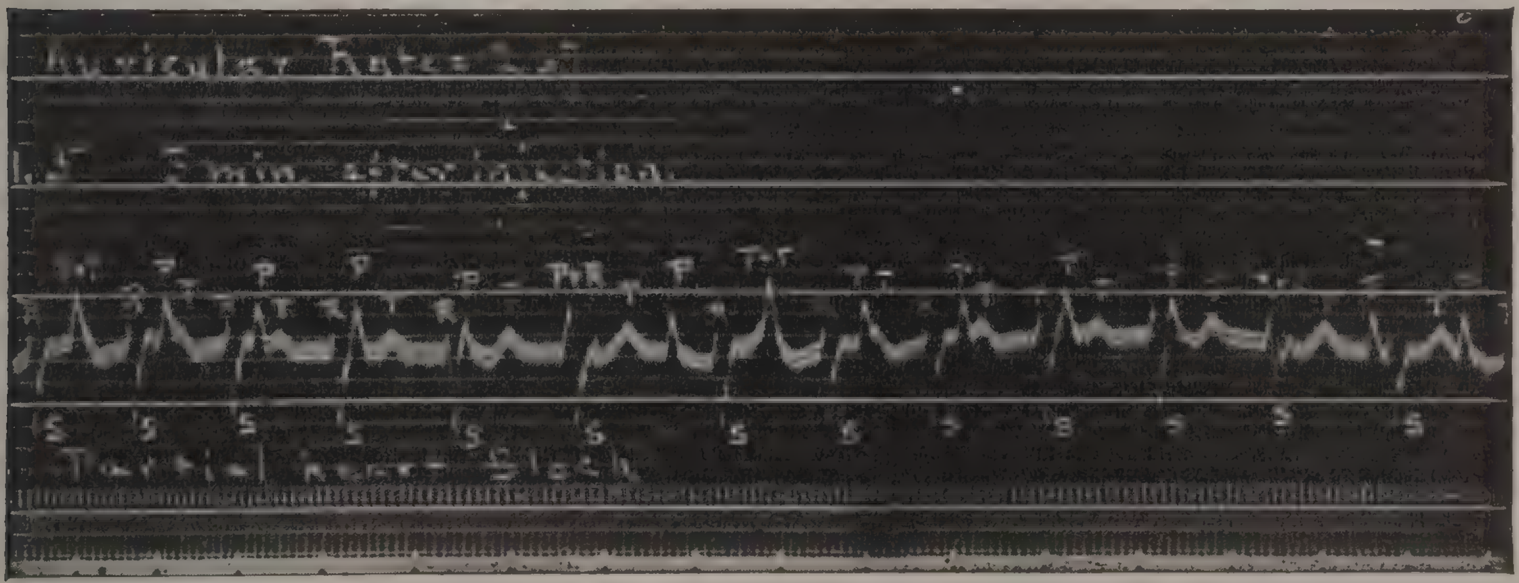

FIG. 4.—DISSOCIATION. ONSET OF PARTIAL AURICULOVENTRICULAR DISSOCIATION. Three minutes after injection of 20 c.c. horse serum into the external jugular vein. Auricular rate, 267. One auricular beat in every eight is blocked. Conduction time varies from 0.12 to 0.28 second. Note diminution of R wave and increase of S wave.

lactic dog, however, acceleration of the heart rate has been but rarely observed during the anaphylactic reaction, and in the case cited above the heart was strongly slowed, from 210, the normal rate, to 184 per minute at the time when auricles and ventricles beat synchronously.

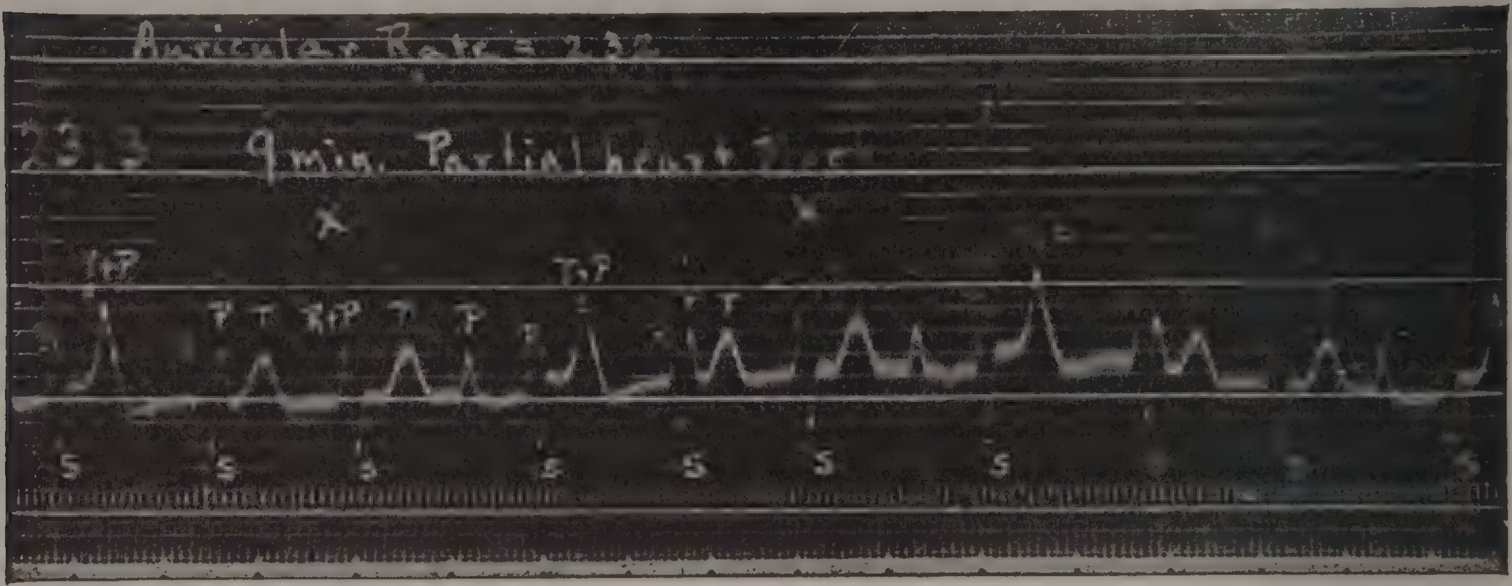

Fig. 5.—Partial Auriculoventricular Dissociation of a Higher Degree. Nine minutes after injection of the horse serum. One auricular beat in every four is blocked; auricular rate, 233. Conduction time varies from 0.14 to 0.26 second.

In addition to changes in the P-R interval the form of the electrocardiograms was altered. Four experiments showed well-defined abnormal ventricular complexes of the same general type. The changes consisted of a diminution of the R waves, a marked deepening and splitting of the S waves, and an exaggeration of the T waves, which sometimes partly fused with the S waves. This change of form, illustrated in Figures 5 and 6, appeared gradually during the anaphylactic reaction, reached a maximum, and then usually returned to the form obtained before the reinjection of the foreign protein. As these changes resemble closely those which Ep-

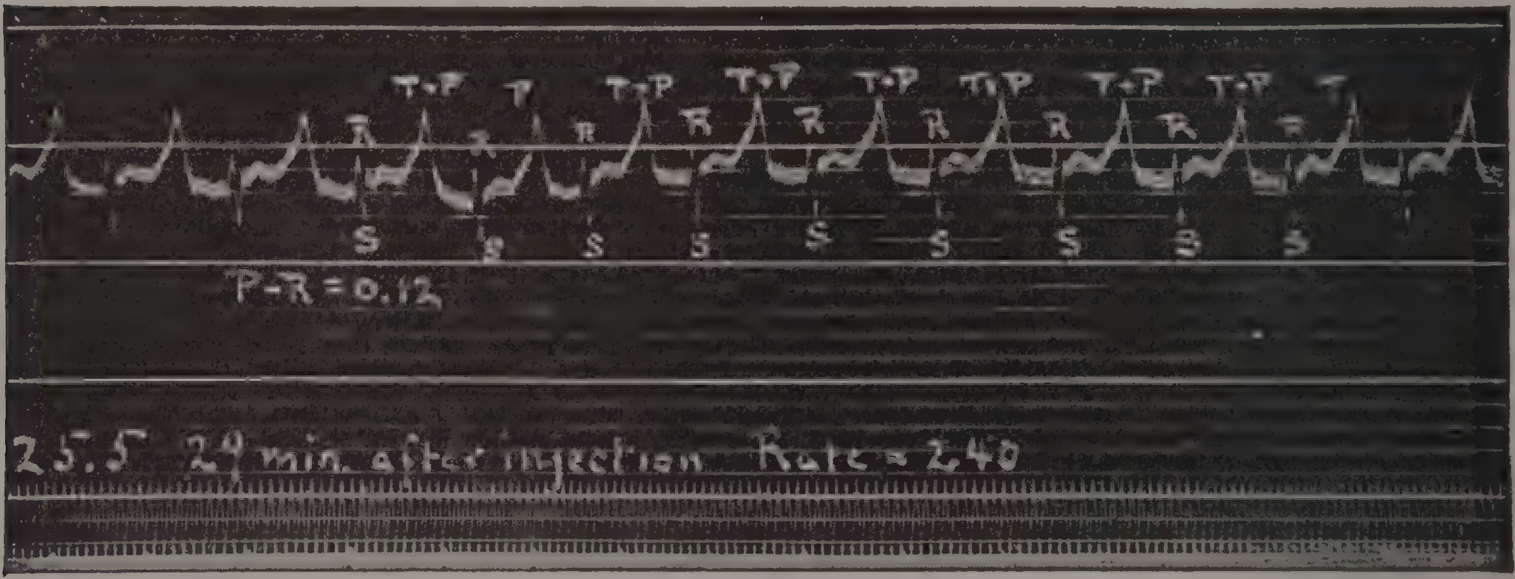

Fig. 6.—Partial Auriculoventricular Dissociation due to Anaphylaxis. Twenty-nine minutes after injection. The nórmal sequential beat has returned, but the form is still abnormal. Conduction time, 0.12 second. Rate, 240.

pinger and Rothberger obtained in the dog when a 20 per cent solution of silver nitrate solution was injected directly into the wall of the right ventricle, or when the limb of the His bundle leading to the right ventricle was cut, it seems legitimate to assume that some alteration occurs in the musculature of the heart during the anaphylactic reaction. This alteration may be caused by the hemorrhages which have been shown to occur into the conducting system during the anaphylactic reaction.

That these deviations from the normal type of the electrocardiogram observed in the dog were true anaphylactic changes was demonstrated by their non-appearance when the animals were again reinjected after the effects of the first reinjection had largely disappeared. Such an injection in the antianaphylactic state produced no effect upon the form of the electrocardiogram, nor upon the blood-pressure. Nor did the same amount of the same foreign serum, when injected into normal dogs, cause changes in the electrocardiogram which even remotely resembled those observed during the anaphylactic reaction.

It might be thought the profound drop in blood-pressure which appears in the anaphylactic dog was the primary cause of the electrocardiographic alterations described above, because a more or less pronounced anemia of the cardiac muscle might ensue as a result of this lowered blood-pressure level. The experiments showed, however, no relationship between the drop of blood-pressure and the appearance and severity of the electrocardiographic alterations. Some of the anaphylactic dogs which exhibited remarkable drops in blood-pressure (145 mm. Hg within 45 seconds in one instance) nevertheless exhibited no change in the form of the electrocardiogram, and the changes in the conduction time (P-R interval), when present, sometimes occurred early, sometimes late, during the state of low blood-pressure. These facts, together with the observations that sudden lowerings of the blood-pressure level by means of amyl nitrite, sodium nitrite, with or without section of the splanchnic nerves, produced no changes in the electrocardiogram which were at all comparable to those obtained during the anaphylactic state, led Robinson and Auer to conclude that the blood-pressure changes themselves did not cause the electrocardiographic changes, but that these changes were of a primary anaphylactic nature.

The alterations observable in the electrocardiogram develop more or less gradually; they usually begin within a few minutes, or even seconds, after the injection; the maximum is usually reached within fifteen minutes, and after the lapse of thirty minutes the electrocardiogram is practically normal. Occasionally the entire process occurs more speedily, and the period of abnormal cardiac activity appears in less than one minute after the injection, persists for a few minutes, and then disappears practically within five minutes, although the animal may succumb. The changes in the heart of the dog are therefore reversible as in the rabbit, but the dog does not apparently show the repeated oscillations between normal and abnormal complexes, such as occur in rabbits, although rhythmic oscillations in the size of the P and T waves do take place.

Rate.—The statements in the literature vary concerning the cardiac rate during the anaphylactic reaction of the dog. Biedl and Kraus report a well-marked increase in the cardiac rate, beginning with the drop in blood-pressure; the tables of Arthus show but slight changes, while Robinson and Auer saw a more or less marked decrease in the majority of their experiments. The differences may perhaps be due to differences in technic, especially anesthesia.

In the cat, Schultz observed that cardiac irregularities appeared shortly after the intravenous injection of horse serum. The right auricle, right ventricle, and pulmonary artery become gorged with blood, while the left side of the heart is practically empty. By massaging the heart and forcing blood through the pulmonary artery several animals survived, according to Schultz. In this connection it may be mentioned that Coca has recently described an anaphylactic stenosis of the pulmonary arterioles in the rabbit.

In frogs sensitized by the injection of 0.1 to 0.5 c.c. sheep serum into a vein, or into the dorsal lymph sac, and reinjected intravenously after one to four weeks, Friedberger and Mita observed that the animals became weak and were unable to hop. Acute death never occurred, but the majority of the animals died within twelve to twenty-four hours. If the chest was opened so that the heart could be inspected and its action recorded graphically, the heart showed a gradually developing strong slowing in the rate of beat due to increased length of diastole, and a marked diminution of the amplitude of contraction. Irregularities of the heart beat were also observed. Normal frogs did not react when the same quantity of sheep serum was injected intravenously.

Experiments upon the Isolated Heart.—Cesaris-Demel and Launoy report the effect of perfusing the isolated hearts of sensitized rabbits and guinea pigs with the protein used for sensitizing. The results of Launoy are especially convincing. This author perfused the coronary vessels of the excised heart of sensitized guinea pigs with 20 per cent horse serum in Ringer-Locke solution. The anaphylactic reaction could be obtained in 90 per cent of the cases, and showed the following characteristics: After the diluted serum reaches the heart the organ contracts more swiftly and the amplitude increases. This phase, which may be only slightly marked or entirely absent, lasts a short time, and is succeeded by an abrupt slowing with or without increase in the amplitude. Now follows an increasing diminution of the amplitude of contractions, together with an increase of the diastolic pauses, which may lead to a stoppage in diastole; the myocardium remains irritable. In most experiments, however, stoppage does not occur, but the heart soon after the initial disturbances beats like a normal organ, although the circulation of the serum solution is continued. This apparent antianaphylaxis can also be demonstrated when the heart of a guinea pig is perfused shortly after the animal has recovered from the anaphylactic reaction; here also the heart continues to beat regularly and strongly when serum is added to the perfusion liquid, and there is no evidence of any disturbance whatsoever. Cesaris Demel's results in the rabbit differ from those of Launoy chiefly in the fact that the Italian observer noted effects in the sensitized heart which were merely more pronounced than similar effects observable in the normal heart after perfusion with horse serum. Launoy, on the other hand, emphasizes the fact that horse serum exerts a depressing action on the sensitized guinea pig's heart, but a tonic action in the normal heart.

On the other hand, Leyton, Leyton and Sowton, after an extensive series of experiments on the excised heart, of normal and sensitized guinea pigs and rabbits (Sherrington-Sowton apparatus), report that 10 to 20 per cent solutions of horse serum cause a marked depression of normal as well as sensitized guinea pig hearts, so that no deductions can be drawn about possible differences in the two classes of text objects. Although they used the same concentration of horse serum as Launoy, it is regrettable that weaker dilutions were not employed with sensitized hearts, especially as their control series of normal guinea pig hearts showed with 5 per cent horse serum only two cases of depression out of six experiments, while 10 per cent solutions yielded depression four times in five experiments and with a 20 per cent strength they report that four-fifths of the hearts were killed at once. It seems possible that a weaker solution than 20 per cent could have been employed with profit in sensitized hearts. The results of Leyton, Leyton and Sowton do not necessarily invalidate the results of Launoy, though the great difference in toxicity between English and French sera remains to be explained.

With rabbits, Leyton, Leyton and Sowton could establish no significant difference between normal and sensitized hearts except that strong dilutions depressed the sensitized less than the normal control hearts. It must be noted, however, that they worked with rabbits only slightly sensitized, for sensitization was produced in their experiments by a single injection of horse serum; the authors nowhere state the dose employed, the site of injection, or the incubation period or periods. This procedure rendered their work on the sensitized heart of rabbits of doubtful value, because rabbits are notoriously difficult to sensitize to a high degree even with multiple, spaced injections, and such a state is necessary in order to obtain the severe cardiac effects described by Auer.

Extracardiac Circulatory System—*Blood-pressure.*—Changes in the blood-pressure during the anaphylactic reaction were first noticed by Richet in 1902. He observed that the intravenous injection of a certain amount of actinotoxin solution did not alter the blood-pressure of a normal dog; but the same dose injected intravenously into a dog who had been treated three or four weeks before with the same actinotoxin now caused a drop in blood-pressure. The drop in pressure developed within two to three minutes after the injection and amounted to 80 to 100 mm. of mercury. As the change in blood-pressure occurred only after some minutes, and as atropin did not prevent it, Richet believed that the heart itself was not affected.

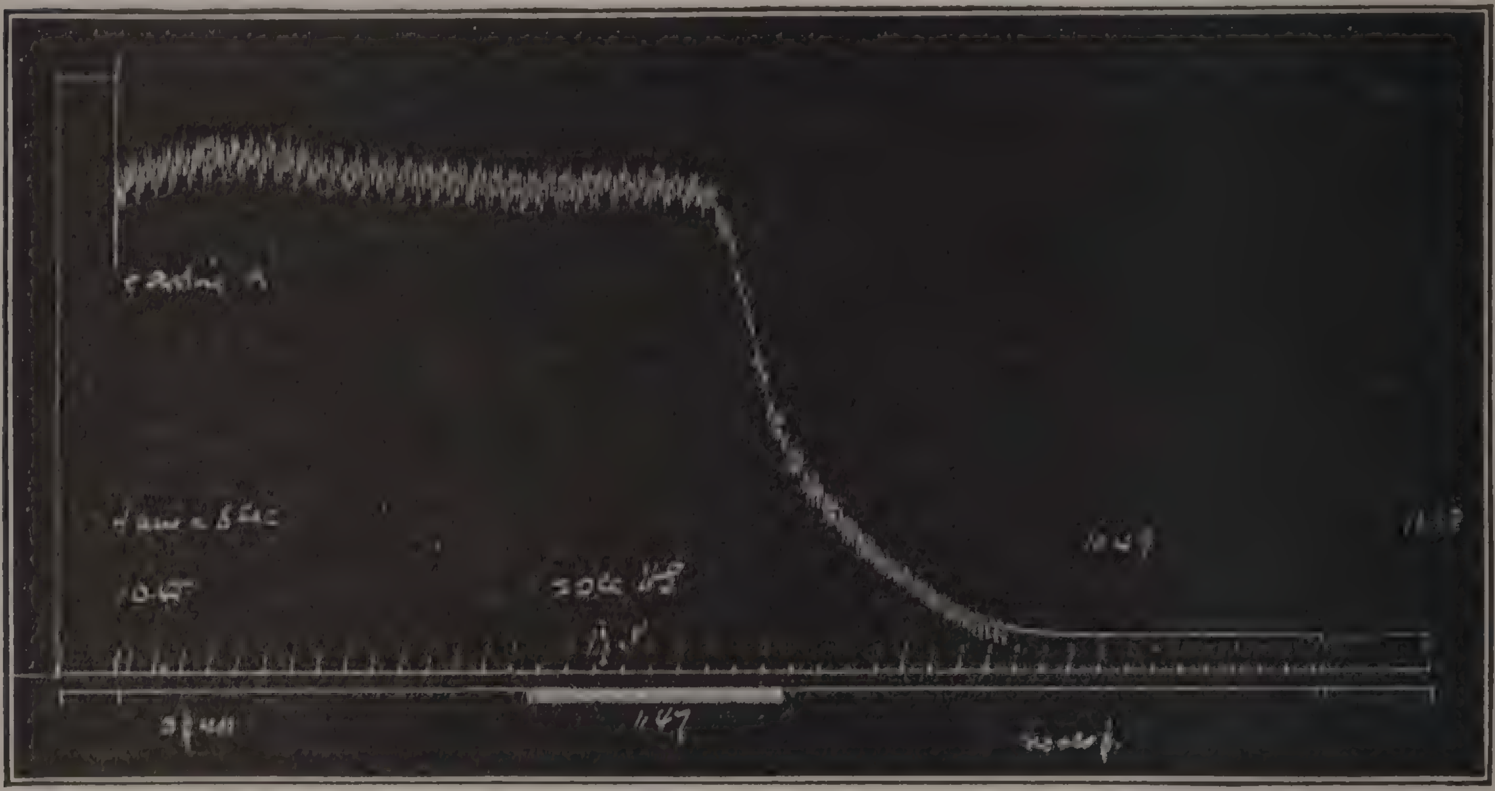

FIG. 7.—ANAPHYLACTIC DROP OF BLOOD-PRESSURE IN DOG. Dog ♀ 9,500; sensitized with 10 c.c. horse serum injected subcutaneously, 5 c.c. in each flank. After thirty days the animal was etherized fully and the blood-pressure recorded by a mercury manometer from the carotid artery; half-saturated sodium sulphate solution filled the connecting tubing. Time recorded in 6-second intervals. Time line, O pressure line.

The reinjection of horse serum is marked by the broad white band below the time line; 20 c.c. horse serum was injected into a jugular vein.

The blood-pressure falls abruptly from 126 mm. to 10 mm. within one minute after the beginning of the serum injection, and spontaneous respiration ceased. The dog succumbed swiftly although intratracheal insufflation was maintained. On immediate autopsy the heart was motionless in diastole and did not respond to mechanical stimuli. The lungs resembled the typical asthmatiç lung found in the anaphylactic guinea pig (see Fig. 2).

The first investigators, however, to demonstrate that a drop in blood-pressure is one of the most constant phenomena in serum anaphylaxis of the dog and rabbit were Biedl and Kraus and Arthus, and their objective findings have been corroborated almost entirely by later investigators.

In dogs the changes were carefully analyzed, especially by Biedl and Kraus. They found that dogs sensitized by the subcutaneous injection of horse or bovine serum and reinjected intravenously after three weeks showed within fifteen to thirty seconds a gradually increasing lowering of the blood-pressure, accompanied by a general excitation of the animal.

The pressure may sink from a normal level of 120 to 150 mm. of mercury (femoral artery) to 40 mm. and less. At this low level the oscillations of the curve due to respiration may be strongly decreased or entirely absent, and the individual pulse beats are much smaller and more rapid than normal. The period of low pressure coincides with the stage of general depression of the dog. If the animal survives, the blood-pressure slowly rises and reaches its normal level within one or more hours. Biedl and Kraus noted a marked parallelism between the degree of blood-pressure depression and the clinical picture: the lower the pressure sinks the severer the picture of intoxication.

Similar observations in sensitized dogs were made by Arthus, who observed that the drop occurred in pronounced cases within fifty to eighty-five seconds after the injection. This drop reached a low level within fifty to eighty-five seconds, and remained stationary for a variable period, at times only a few minutes. Arthus observed repeatedly that the original level was reattained ten to twenty-five minutes after the injection; this result is probably to be ascribed to the relatively low sensitization of Arthus' animals.

In the dog there is no marked difference except one of degree in the blood-pressure curve obtained from those which survive and those which succumb.

In rabbits sensitized subcutaneously with horse serum and reinjected intravenously, and which survived an intravenous reinjection, Arthus observed as a rule, a very similar blood-pressure picture: fifteen to thirty-five seconds after the injection the carotid blood-pressure falls from the normal level of 100 to 120 mm. of mercury to the 34 to 48 mm. level. This level is reached within fifteen to forty-five seconds after the pressure begins to fall, and is maintained for about twenty to twenty-five minutes. Arthus also observed a marked diminution of the respiratory and cardiac oscillations during the drop in pressure, so that the curve almost appeared as an unbroken line (mercury manometer).

Arthus does not mention the occurrence of any rise of blood-pressure in the rabbit immediately after the injection. Such a rise, however, was noted fairly frequently by Loewit and by Auer. This rise was moderately slow, rarely exceeded 20 mm. of mercury, persisted after the injection, and could not be attributed to the mechanical effect of the injection itself.

If a rabbit succumbs acutely to the reinjection, the blood-pressure curve is somewhat different from that just described. Shortly after the reinjection of horse serum the blood-pressure often begins to rise, the pulse pressure increases, the respiratory oscillations become less or disappear, and the heart slows moderately. This rise, which may be 20 mm. and more, does not last longer than one minute, and is often broken by a series of drops which look like vagus pulses, though they are also obtained in animals whose vagi have been sectioned. Then the pressure slowly sinks, the pulse pressure decreasing strongly, while the rate usually increases. This drop may continue until within one to two minutes the 10 to 15 mm. level is reached, and after five to six minutes no heart beats are discernible on the curve, even though the record be taken with a membrane manometer. During the final drop in this type of curve the record always shows arrhythmias and marked sudden changes in rate and in pulse pressure. A modification of this type is introduced when the abrupt increase in the pulse rate, which occurs after the initial slowing, temporarily delays and slows the drop in blood-pressure, but here also the membrane manometer records no beats within five to ten minutes after the reinjection. Still another modification of the curve is obtained when the heart abruptly stops beating, which occurs now and then. All these forms of blood-pressure curve are obtainable from animals which have been curarized, and whose vagi have been cut in the neck previous to the reinjection (Auer).

In the cat the blood-pressure curve is quite similar to that obtained in the dog, according to Schultz, but the reaction is apparently more severe, for his curves show practically no pulse beats, even before the lowest level is reached.

In the guinea pig which dies acutely, the blood-pressure rises gradually during one or two minutes after the injection. This rise varies from 20 to 60 mm. of mercury, and is usually associated with an increased pulse pressure and slight alterations in rate; then a gradual drop in the blood-pressure follows, usually with a marked slowing of the heart, and the 10 mm. level is usually reached within five to ten minutes after the reinjection. The pulse pressure decreases during the drop, and at the lowest level the individual heart beats can hardly be distinguished, even when recorded with a membrane manometer (Auer and Lewis; Biedl and Kraus; Loewit).

The course of the blood-pressure curve in a non-fatal reaction of the guinea pig has not been described as far as the writer is aware.

From the preceding descriptions two general types of blood-pressure reaction can be distinguished: (1) the abrupt deep fall of blood-pressure which occurs within one minute after the injection and reaches its maximum within another minute or two, such as occurs in dogs and cats; and (2) the slower, more protracted lowering of the blood-pressure usually preceded by a rise such as occurs in the fatal reaction of rabbits and guinea pigs. To this group the writer would also add on the basis of his experiments the blood-pressure reaction of non-fatal anaphylaxis in the rabbit, although Arthus' description indicates a close likeness to the type which occurs in the dog. These different types of blood-pressure reaction are apparently caused by the interplay of different mechanisms.

Biedl and Kraus came to the conclusion that the blood-pressure drop in the dog was caused by a transitory paralysis of the peripheral vasomotor apparatus in the splanchnic area. They excluded the heart as a possible factor on theoretical grounds, but were substantially correct in this, for the direct registration of ventricular activity by Eisenbrey and Pearce showed no decrease in rate and strength during the early stages, and the electrocardiographic studies of Robinson and Auer revealed no definite relation between a pathological activity of the heart and the abrupt decrease in arterial pressure; moreover, a number of their dogs exhibited a profound blood-pressure effect without any alteration of the electrocardiogram. It is legitimate, therefore, to exclude the heart as a vital factor in the production of the blood-pressure drop. Biedl's and Kraus' experimental proof was as follows: during the stage of low blood-pressure in the dog stimulation of the peripheral stumps of the splanchnic nerves gave no rise in blood-pressure; the intravenous injection of 1 to 2 c.c. of adrenalin had only a slight or no effect in the early stage of arterial depression, though a gradually increasing rise of pressure was obtained as the dog recovered; the injection of $BaCl_2$, however, raised the blood-pressure, even when injected very early in the stage of arterial depression. Since adrenalin is believed to act chiefly upon the vasomotor endings, while $BaCl_2$ acts by stimulation of the vascular musculature itself, Biedl's and Kraus' inference was well founded, and has been corroborated and amplified by other investigators, especially Pearce and Eisenbrey. Pearce and Eisenbrey also demonstrated that, with the decrease in arterial pressure, the kidney, intestine, and spleen show a decrease in volume, while the blood accumulates in the large venous trunks and in the liver. The accumulation of blood in the liver was graphically registered by Edmunds, and this venous congestion of the liver has been explained by Simonds as due to a tonic contraction of the musculature of the hepatic veins and their branches. Pearce and Eisenbrey characterize the condition of anaphylactic low blood-pressure in the dog as a bleeding into the veins of the abdomen, analogous in many respects to surgical shock.

The anatomical basis for this congestion of the liver in the dog during the anaphylactic reaction has been furnished by Simonds. This author finds that the hepatic vein of the dog differs from that of the guinea pig, rabbit and other herbivora by possessing a relatively enormous amount of smooth muscle in its walls. According to Simonds the fundamental physiological reaction in anaphylactic shock of the dog is a spasm of the smooth muscles in the walls of the hepatic vein and its branches.

For the cat Schultz states that the drop in blood-pressure is caused by a weakening of the heart, especially the right side, which becomes distended with blood and loses its power of contraction almost immediately after the horse serum is injected intravenously, together with a constriction in the divisions of the pulmonary artery so that little blood enters the left auricle. Schultz explains the venous congestion of the splanchnic area as due to back pressure, because the right side of the heart is unable to empty itself on account of its weakness and the increased resistance in the pulmonary arterial circuit. Similar results were obtained by Schultz after clamping arteries and veins so that the circulation was practically limited to the heart-lung circuit. The evidence undoubtedly shows that the heart is strongly affected in the cat, but it does not prove that the splanchnic congestion is purely a passive effect. Moreover, it must be emphasized that Schultz does not discriminate sharply between the effects observed on first injection of horse serum in cats and those which occur when sensitized animals are reinjected; he apparently considers the primarily toxic action of horse serum in cats as qualitatively identical with the action which the serum produces when injected into cats sensitized with this serum.

This back pressure theory of Schultz does not hold for the dog, for Pearce and Eisenbrey saw no distention, but a collapse, of the right side of the heart during the blood-pressure drop, and Edmunds at that time observed only a transitory rise of pressure in the pulmonary artery and pulmonary veins, followed immediately by a drop, indicating no stenosis in the pulmonary circuit.

In the acutely fatal anaphylactic reaction of the rabbit the heart plays an undoubted rôle in the causation of the drop of blood-pressure, for the gross muscular changes which strongly reduce, and even abolish, cardiac contractility must obviously have this effect. It should be remembered that some of these cardiac effects are apparently secondary to a strong anaphylactic stenosis of the pulmonary arterioles according to Coca. It is interesting that the rabbit shows changes similar to those Schultz described in the cat.

What rôle the splanchnic motor endings play in the rabbit has not been established with certainty; but Scott observed that an intravenous injection of adrenalin during the stage of low pressure produces only a transitory rise of pressure without amelioration of the symptoms. That some effect is exerted upon the splanchnic area is also indicated by the often intense engorgement of the liver and of the portal system of vessels. Perhaps the anaphylactic intoxication in the rabbit does not act equally upon the heart and the splanchnic area, and the different degrees with which they respond may explain the different types of blood-pressure drop which have been described for this animal. The initial rise of blood-pressure may possibly be due to a stimulation of the vasomotor center, as Loewit suggests, but this is not established with certainty.

In the guinea pig the blood-pressure changes are probably secondary to the asphyxia which develops within a few seconds after the reinjection. The heart, although it often shows extensive hemorrhages, shows no weakness, but almost invariably beats powerfully on inspection when the blood-pressure is not more than 10 to 20 mm. of mercury, and drives blood some inches into the air when the pulmonary artery or the aorta is cut open. The splanchnic area often shows marked engorgement, but this is by no means invariable; in the same series of animals one may observe the small intestines quite pale and contracted and the mesenteric vessels practically empty, while others show a pronounced congestion, especially of the mesenteric vessels.

In general it may be said that in the guinea pig, as well as the rabbit, the rôle of the splanchnic area as a factor in the blood-pressure has not been sufficiently studied, and the warning of Biedl and Kraus not to identify indiscriminately the lowering of the blood-pressure during anaphylaxis in the dog, rabbit, and guinea pig is justified.

Other Changes in the Circulatory Apparatus.—Schultz and Jordan observed that the arterioles in the anaphylactic lung of the guinea pig show a series of constrictions so that the artery looks beaded, and the lumen is practically obliterated. This condition was noted in normal as well as anaphylactic lungs.

Huber and Koessler also describe beading of the arterioles of the Schultz and Jordan type not only in the anaphylactic guinea pig lung but also in a human subject suffering from asthma.. These authors made a careful histological study of numerous lungs obtained by autopsy from asthmatic patients and determined that the walls of the smaller bronchi and bronchioles in the asthmatic individual are thicker than those of comparable structures in the non-asthmatic; this thickening, though involving all layers, is especially outspoken in the muscle layer as demonstrated by their statistical graphs.

Similar observations have been described by Fröhlich in the mesenteric arterioles and small veins of frogs. The frogs had been sensitized by the injection of 0.1 to 0.5 c.c. of pig or sheep serum into the dorsal lymph sac, and the test was made eight to fifteen days later by applying a dried flake of the homologous serum locally on the exposed mesentery of the curarized animal. Microscopical examination showed gradually developing contraction rings of the arteries and veins. Fröhlich also observed changes in the capillaries in the neighborhood of the serum; after ten to fifteen seconds they became maximally dilated and irregularly contoured; some of the capillaries were full of red corpuscles, while others were filled with clear plasma. Beading of the veins may also be observed quite frequently in the small veins of the gut, mesentery, and diaphragm of guinea pigs and rabbits who succumb acutely to the anaphylactic reaction; it is usually especially obvious in the large veins which border the central tendon of the diaphragm (Auer). It is probable that these beadings play a rôle in the production of the superficial hemorrhages of the heart, spleen, lung, and gastro-intestinal canal described by Gay and Southard.

A marked dilatation of the conjunctival vessels has been described by

Denecke in dogs sensitized and intoxicated by the intravenous injection of egg-white. Within five to seven minutes after the reinjection the conjunctival vessels dilate strongly, and the dilatation may persist for half an hour.

Muscle System—*Smooth Muscle of the Viscera.*—The smooth muscle of the guinea pig's lungs, or the musculature of the arteries and veins, are not the only places where an anaphylactic reaction occurs in smooth muscle. Schultz, in an important series of investigations, was the first to show that smooth muscle in general from the intestine, bladder, and arteries exhibits an anaphylactic reaction, but unfortunately he did not differentiate clearly between a true anaphylactic reaction obtainable only in a sensitized animal and the similar reaction which native sera sometimes exert on normal, unsensitized animals. As Schultz's work was corroborated, corrected, and amplified later by Dale, and as Dale deals only with true anaphylactic phenomena, the following description is based on Dale's work.

Dale employed the horns of the uterus from virgin guinea pigs sensitized with various proteins, chiefly horse serum, because he found this organ responded more regularly and delicately than any other smooth muscle preparation from the guinea pig. After suspension in warm oxygenated Ringer solution, and connection with a writing lever, the horn soon loses tonus and exhibits a small, fairly rhythmical series of contractions. The irritability of the preparation remains practically unimpaired for some hours. If to such a preparation the protein used for sensitization is added, the uterus responds with a strong tetanic contraction, which is maintained a varying length of time, and is followed by a slow relaxation. The doses necessary to obtain specific responses were very small; curves illustrate the article which show a strong contraction when 0.0001 c.c. of horse serum was added to the bath volume of 50 c.c. Ringer solution, which represents a dilution of 1:500,000. Even greater dilutions, for example, 1:1,000,000 of horse serum, produced a definite, though not maximal, response. Dale states that, as a rule, the uteri of animals sensitized by small doses of horse serum and tested after twelve days show a strong response to dilution of horse serum above 1:100,000.

After the sensitized uterus preparation has responded maximally to the protein used for sensitization it does not contract again, after relaxation and change of bath solution, when the same protein is added in even stronger concentration; it is desensitized or antianaphylactic. A *non-specific* contraction may, however, be obtained by the addition of sera containing toxic constituents (fresh horse or guinea-pig serum), and such contractions are also obtained when the same sera are allowed to act upon normal non-sensitized uteri.

Dale was also able to resensitize his preparation after it had become specifically refractory or antianaphylactic. This was accomplished by allowing the uterus to remain for several hours in an oxygenated 10 per cent solution of fresh serum from a guinea pig sensitized with horse serum. After thorough washing with Ringer solution this preparation gave a definite response when subjected to the action of a 1:400 solution of horse serum. A further test showed that desensitization or antianaphylaxis had now again been established. Passive sensitization of the normal uterus was, however, only obtained when the organ was perfused through its arterial system for several hours with a 20 per cent solution of serum obtained from guinea pigs sensitized to horse serum. On testing, the uterus horn responded typically to a horse serum dilution of 1: 500 Ringer, while the control horn, which had not been perfused, showed no effect whatsoever.

The uterine preparation, therefore, permits the demonstration of many of the fundamental phenomena of anaphylaxis; passive sensitization, specific reaction, antianaphylaxis, and even the period of incubation is indicated.

During the anaphylactic reaction there are a number of other phenomena which are referable to a tetanic contraction of smooth muscle. All observers have noted the roughening of the fur in anaphylactic guinea pigs, and a similar effect may be observed in rabbits. This erection of the hair may be due to an anaphylactic contraction of the pilomotor muscles, though no rigid proof has yet been given.

The scrotum of sensitized dogs when reinjected often shows a slow, powerful contraction which produces marked corrugations of the scrotal sac (Auer).

The iris may show a strong constriction during the anaphylactic intoxication. Schultz observed that the pupils of a normal non-sensitized cat diminished to a slit after horse serum had been injected intravenously. A similar strong effect may be observed in rabbits sensitized to horse serum. When the antigen is reinjected the pupils often become pin point in size.

The tetanus produced in smooth muscle by the anaphylactic reaction seems to last about the same length of time, no matter what the origin of the muscles. Dale's experiments with the uterine horns of guinea pigs show that approximately five to twenty minutes elapsed before the structure was again normally relaxed. A similar interval is to be noted in Schultz's work with intestinal smooth muscle. The scrotal sac assumes its smooth surface approximately five minutes after the contraction has begun. The contraction of the iris lasts from five to fifteen minutes when the innervation is intact, and about thirty minutes when the dilator pupillæ is denervated by extirpation of the superior cervical ganglion. The time interval for the bronchial muscle cannot be judged accurately, but the anaphylactic lung of the guinea pig largely maintains its distention for days when kept in the ice-chest. If the anaphylactic lung of the guinea pig is kept at room temperature a definite diminution in size is observable within one hour as a rule (Auer).

Striated Muscle.—A number of functional and anatomical changes in the heart and striated muscles of anaphylactic animals, chiefly guinea pigs and rabbits, have been described by Gay and Southard, Auer, Beneke and Steinschneider, Loewit, and von Worzikowsky-Kundratitz. Gay and Southard in 1907 observed fatty changes and hemorrhages in the heart and voluntary muscles of guinea pigs which succumbed to the reinjection. In addition the voluntary muscles of forelegs and hind legs showed swelling and loss of striation microscopically. Changes in the heart muscle of rabbits which succumb acutely have already been considered; they consist chiefly of a loss of irritability of both ventricles, together with a rigorlike alteration of the right ventricle, which is not found in the left ventricle. Rigorlike changes may also be observed in the diaphragm and thigh muscles of the rabbit (Auer). A speedy development of rigor in the guinea pig's heart has been described by Loewit, though this does not occur abruptly during life as in the rabbit, but only after the heart has gradually stopped beating. The histological examination of guinea pigs' hearts by von Worzikowsky-Kundratitz showed findings which were quite similar to those observed by Beneke and Steinschneider in the diaphragm and skeletal muscles of anaphylactic guinea pigs, though quantitatively less marked. Beneke and Steinschneider describe a granular waxy degeneration of the muscle fibers, while Worzikowsky-Kundratitz saw a waxy degeneration only occasionally, the most constant change in his experience being a cloudy swelling with granular degeneration. The degeneration was most pronounced in the diaphragm, where the majority of the muscle fibers look swollen, show a loss of striation, and present a homogeneous, cloudy, occasionally granular appearance. Beneke and Steinschneider considered these changes the direct result of an anaphylactic poison, but Wells pointed out that this interpretation is improbable because a typical waxy degeneration of striated muscle may be obtained by a lengthy stimulation of its motor nerve, and is attributable to the formation of sarcolactic acid. As anaphylactic guinea pigs die of an asphyxia associated with violent convulsions, conditions are favorable for a maximal accumulation of sarcolactic acid in the muscles, which Wells has experimentally shown to be capable of producing the histological changes described.

As the histological alterations are much more pronounced in the anaphylactic animals than in those killed by peptone, nucleic acid solution, or primarily toxic sera, von Worzikowsky-Kundratitz is inclined to consider the intensity of the reaction as characteristic of the anaphylactic intoxication.

Gastro-intestinal System.—The stomach and intestines exhibit obvious anatomical and functional alterations during the anaphylactic reaction, the character of which varies with the animal species employed. In the dog, Richet, Biedl and Kraus, and Pearce and Eisenbrey noted the following effects:

The first symptom usually is retching and vomiting, which may begin within a few seconds after the animal has been injected. The severity of this vomiting seems especially great in dogs reinjected with poisonous animal extracts, for Richet describes the vomitus as sometimes fecal and even mixed with blood. A few minutes after the onset of the vomiting, evacuations of the bowel occur which are fluid and sometimes stained with blood. The bladder is also emptied. In this stage the animal is usually lying limply on the floor, the respiration is usually deepened, but, as a rule, no strong dyspnea is present. The animal does not respond to a call, but is not unconscious; it merely exhibits a marked muscular weakness. In the average dog sensitized with horse serum the attacks of vomiting become gradually less severe, and may disappear within fifteen minutes after the injection. The diarrhea, however, may persist for many hours. On autopsy Pearce and Eisenbrey observed swollen and hemorrhagic areas in the mucosa along the greater curvature of the stomach, and a similar condition in the duodenum and upper small intestine; the Peyer's patches were dark and elevated, but showed no hemorrhages; the colon was also hemorrhagic.

In the rabbit vomiting cannot occur because the stomach content is semisolid but the intestine and cecum show marked peristaltic movements which are easily visible through the relaxed abdominal walls of the animal. This increased peristalsis is not limited to the small gut and cecum, but also occurs in the colon, for shortly after the injection dry well-formed scybala are passed. The quantity of feces evacuated varies considerably in different rabbits; a considerable number of pellets may be obtained from one rabbit, while its mate, which was treated in exactly the same way, passes only a few.

Peristalsis is best observed in rabbits which have been stretched out on their backs and the abdominal hair clipped. The normal peristaltic and antiperistaltic waves of the cecum are markedly increased in strength and frequency, and evidences of small-intestinal activity are seen in the left upper and right lower quadrants of the abdomen. The intestinal activity due to the reinjection usually begins shortly after the intravenous injection during the stage of rapid shallow respiration. Arthus, who first observed the increased peristalsis in the rabbit, states that the pellets are absolutely normal, and that there is no diarrhea. Auer has observed the same, but Scott has described the appearance of a thin watery diarrhea. Autopsy does not show any pronounced changes as a rule: there is slight or no peristalsis; the gut may be moderately congested, but the mesenteric vessels, especially the veins, are usually large and full. The surface of the small intestine and cecum may show some hemorrhages. Scott describes a marked capillary engorgement with minute hemorrhages, which are especially noticeable in the intestinal villi.

In the guinea pig gastro-intestinal symptoms are still less marked than in the rabbit. True vomiting does not occur, but in animals which have been stretched out on their backs for examination stomach contents may often be observed in the mouth during the violent asphyctic convulsions which the reinjection causes. This material has probably been forced out of the stomach by the strong compression which the stomach suffers when the costal margin and sternum are drawn inward during an inspiratory attempt, and the increased negative pressure in the thorax, and consequently esophagus, must also aid in bringing material from the stomach back into the mouth. Fecal pellets begin to appear usually after the first signs of asphyxia develop, but the entire quantity passed is usually small. The pellets are always well formed and no true diarrhea has been recorded. Visible peristalsis occurs after the animal has succumbed and the abdominal walls are relaxed. When the abdomen is opened the small intestines at times contract violently, but coördinately, and a strong wave of contraction which constricts and blanches the gut to a gray cord sweeps swiftly down, driving the fluid contents before it with such speed that the loop of intestine rises up and remains standing for a second or so like a wire spring because the relaxation takes place with some slowness. While this type of intestinal peristalsis (Rollbewegungen of Houkgeest, and peristaltic rush of Meltzer and Auer) is surely partly due to asphyxia, it seems probable in view of the work of Schultz and Dale that it is also partly an anaphylactic phenomenon.

The gut itself is usually found moderately congested, but in many instances it may be quite pale and relaxed without any noticeable hemorrhages at all.

Whether or not hemorrhages are pronounced in the gastro-intestinal canal (Gay and Southard) seems to depend to some extent upon the speed with which death results; the more rapid the death the less prominent the hemorrhages often are. After intraperitoneal reinjection the guinea pig usually dies within an hour, and Gay and Southard found that gastric hemorrhages were especially frequent, though not necessarily constant. These gastric hemorrhages, varying in size from a pin point to 2 cm. in diameter, occur chiefly on the greater curvature, and are submucous or show definite erosion, with hemorrhages into the stomach. The same authors also observed hemorrhages in the cecum, lung, spleen, adrenals, heart, and diaphragm. Histologically Gay and Southard describe minute interstitial hemorrhages due to endothelial fatty changes in the capillaries.

According to Auer the gastric hemorrhages observed in the guinea pig are caused by autodigestion of locally asphyctic areas in the stomach mucosa; the local asphyxia is produced by powerful, temporary, peristal toid contractions of mucosal capillaries, as evidenced by the histological picture.

Glandular System.—Anatomical and functional changes have been described in glandular structures. Modrakowski observed increased secretion of pancreatic juice in the dog during the anaphylactic reaction. The secretory activity of the tear and salivary glands is also somewhat augmented.

The adrenal glands of guinea pigs which have succumbed or recovered from an anaphylactic action show an intense diffuse green coloration after fixation in Müller-formalin, while controls exhibit only a slight green color, according to Ucke. This author tentatively advances the suggestion that the drop in blood-pressure is due to a fixation of adrenalin in the glands. An anatomical foundation for this view is perhaps furnished by the observation of Wells, in his recent review, that the human central adrenal veins show a large amount of muscle tissue which is apparently greater than in other veins of corresponding caliber.

In human bronchial asthma, Huber and Koessler have called attention to the striking hypertrophy of the bronchial mucous gland system.

Necrosis of varying types has been described in the kidney and liver by Gay and Southard and others. Longcope has recently again investigated this question in the guinea pig, rabbit, cat, and dog. All the animals were sensitized by repeated injections, usually subcutaneously, of horse serum or egg-white. The toxic reinjection was administered usually intravenously. Longcope observed especially the kidney, and records practically similar changes in all species of animals examined: marked nephritis with degeneration and necrosis of the loops of Henle, collecting tubules, occasionally also the convoluted tubules. These alterations were accompanied by a round-cell infiltration of the connective tissue, and later stages showed the new formation of connective tissue. The glomeruli exhibited acute and chronic changes. After intraperitoneal injections marked inflammatory reactions of the peritoneum were obtained.

The functional investigation of the rôle of the liver in the causation of the anaphylactic reaction has yielded some interesting and suggestive results as far as the dog is concerned. The liver is negligible for the production of an acute anaphylactic reaction in the sensitized guinea pig, rabbit, and cat: the anaphylactic lung may be obtained after the liver and intestine are excluded by ligatures; the excised sensitized lung itself responds typically when ventilated and perfused with the protein used for sensitization (Dale); in the rabbit the typical heart effect may be obtained when the central nervous system is destroyed and the thoracic aorta and inferior vena cava are clamped (Auer); and in the cat a similar procedure does not prevent the production of cardiac irregularities and stoppage (Schultz).

In the dog, however, the liver appears to play an important rôle both in sensitization and intoxication. Manwaring was the first to call attention to the fact that a removal of practically all the viscera, except the liver, of a dog sensitized with horse serum does not prevent the occurrence of a pronounced drop in blood-pressure associated with incoagulability of the blood when the animal is reinjected. Manwaring then excluded only the liver from the general circulation by ligating the vena cava above and below this organ, and maintained the circulation by placing T cannulæ in the inferior vena cava and portal vein and leading the tubing to the external jugular vein; all the viscera remained in normal connection, therefore, until the ligatures were tied. The injection of hirudin was necessary in order to prevent clots. Four dogs out of seven showed no drop in blood-pressure when the horse serum was injected intravenously after closing the ligature wires, but showed atypical slow drops in blood-pressure when the ligatures were loosened. Manwaring also states that shock may usually be obtained if the ligatures are opened within three minutes after the injection; if the time interval, however, is five minutes or more no shock develops, but another injection now produces a drop in blood-pressure.

Voegtlin and Bernheim corroborated Manwaring's results and improved his technic by employing sensitized Eck-fistula dogs combined with a ligation of the portal vein near the hilus of the liver; in these dogs clamping of the hepatic artery would exclude the liver completely. After the hepatic artery was clamped the authors never obtained any drop of blood-pressure when the horse serum was injected, but a drop developed when the clamp was removed.

Voegtlin and Bernheim also made the important observation that three of the Eck-fistula dogs which were sensitized *after* the operation failed to show any anaphylactic reaction on reinjection. This has been corroborated by Denecke. The latter investigator failed to obtain an anaphylactic reaction in eleven Eck-fistula dogs which had been sensitized by the intravenous injection of 1 c.c. egg-white and tested after three weeks by the intravenous injection of 10 c.c. egg-white; there were no gastro-intestinal symptoms, no leukopenia, and no drop in blood-pressure (the latter was tested only in two cases). If, however, the Eck-fistula was established three weeks after sensitization with egg-white, then the reinjection caused vomiting, bloody diarrhea, and in the one instance tested the blood-pressure dropped to 30 mm. Hg. The liver, therefore, seems to be necessary to obtain sensitization in the dog.

In a further series of experiments Denecke brought forward evidence that a relation apparently exists between the concentration of the foreign protein reaching the liver and the degree of sensitization. He observed severe effects, for example, when dogs with a reversed Eck-fistula (Eck-fistula dogs with the inferior vena cava ligated; all the blood of the lower half of the body therefore passes through the liver) were sensitized and later intoxicated by the injection into a vein of the *hind* foot. If, however, the reversed Eck-fistula dogs were sensitized by an intravenous injection into the anterior part of the animal, and intoxicated after an appropriate interval, by an injection into a vein of the hind foot, only mild symptoms appeared. Denecke explains this result by assuming that a greater degree of sensitization occurs in those dogs where the egg-white reaches the liver in a less dilute state; in the reversed Eck-fistula dogs the protein would, of course, be less diluted before reaching the liver if the sensitizing dose were incorporated through a vein of the hind foot than if the injection were made into the anterior half of the animal. Some remarkable liver alterations have been noted by Hashimoto and Pick; these authors describe a doubling or even trebling of the non-coagulable nitrogen in the guinea pig's liver after mere sensitization by horse serum; they also observed that the livers of the same species obtained after acute anaphylactic death show only slight or no postmortem autolysis.

Urine.—Pfeiffer reports that the urine of guinea pigs which suffered a severe subacute anaphylactic reaction is toxic to normal animals of the same species. The intraperitoneal injection of 1 to 2 c.c. causes severe symptoms resembling those of anaphylaxis; subcutaneous injection of this urine causes necroses similar to Arthus' phenomenon.

Blood and Lymph System—*Blood.*—A number of changes occur in the chemical and physical behavior of the blood as well as in the blood-cell picture during the anaphylactic intoxication. The most striking alteration is the reduction or loss of coagulability, which is most pronounced in the dog, less in the rabbit, and least in the guinea pig. If arterial blood is removed from the dog during the height of the anaphylactic reaction it remains uncoagulated for hours, or even days (Biedl and Kraus, Arthus). When a clot finally forms it is usually soft and does not retract normally. As the coagulation proceeds so slowly the red corpuscles settle completely, leaving a clear supernatant plasma, which sometimes shows many fine floccules. The "buffy coat" is barely indicated. In the rabbit Arthus observed that clotting was delayed from one-half to one hour, while normal rabbit's blood clotted within ten to twelve minutes. Both in the rabbit and dog, as these animals recover from the anaphylactic reaction, the blood gradually regains its property of coagulating. In the guinea pig no well-marked delay in coagulation is demonstrable if the blood is taken immediately after acute death. If the guinea pig does not succumb acutely, a delay in coagulation occurs. Sirenskij reports that the blood of guinea pigs, sensitized with horse serum and reinjected intraperitoneally, examined fifteen to forty-five minutes after the toxic injection, showed a definite delay in coagulation (Brodie's chamber); the delay was longest in protracted cases. The fibrin-ferment content diminished slowly after the reinjection, but was almost invariably largely reduced in amount after forty-five minutes. No alteration in the Ca or Mg content was observed by Sirenskij, but the fibrinogen seemed to be decreased in amount after the anaphylactic reaction.

The diminished coagulability of the blood may be considered as a secondary effect of the reinjection, for De Waele states that the parenteral injection of any foreign protein causes as a primary and immediate reaction of the organism a thromboplastic action and an antithrombin secretion, which latter is perhaps referable to the liver; the two phases, one aiding coagulation, the other delaying it, follow each other in a wave-like fashion. However this may be, probably every investigator has observed marked fluctuations in the non-coagulability of the anaphylactic blood, both in the dog and rabbit. There are no records that any one has ever observed a hastened clotting of the blood when an originally non-toxic protein was employed for reinjection. Such hastened clotting may occur: Auer noticed that one rabbit of a series of five which had been sensitized by repeated subcutaneous and intraperitoneal injections of horse serum died acutely on intravenous injection, while the other animals reacted to the same serum with moderate anaphylactic symptoms. Immediate autopsy of this animal showed that the heart was not beating and had stopped in diastole; the right auricle and ventricle were filled with a blood-clot; the superior vena cava and its branches, the abdominal vena cava, and renal vein were full, round, and filled with a solid clot; the veins of the portal system, however, contained no clot, but fluid blood; the liver was dark and rich in fluid blood on section. The right ventricle showed the typical toughness of its endocardial surface to a marked degree. There was no pulmonary edema and no foam in the trachea.

It was mentioned before that the antithrombin was perhaps secreted by the liver; but it must be noted that the blood in the rabbit can show a typical reduction in coagulation when not only the liver, but all sub-diaphragmatic structures, are excluded. Auer reports that a sensitized rabbit whose aorta and inferior vena cava had been clamped above the diaphragm after destruction of the entire central nervous system, and kept avile by artificial respiration, showed marked differences after reinjection in the coagulability of the blood when taken above or below the clamp; above, the blood did not coagulate during thirty minutes, while the blood in the veins below the clamp clotted firmly in fifteen minutes. The heart showed the alterations typical for the acute reaction in this animal. The liver thus cannot be the sole source of antithrombin in the anaphylactic rabbit.

Complement.—A large number of researches deal with the rôle the complement plays in the anaphylactic reaction, and this has been especially investigated by Friedberger. While in general the complement content of the blood sinks more or less during the anaphylactic reaction, this loss of complement does not go parallel with the severity of the anaphylactic reaction. The blood of a guinea pig which dies acutely may show no, or only a slight loss of complement (Sleeswigk). Loewit and

Bayer produced an intravital fixation of the complement in a sensitized guinea pig by injecting an anticomplement serum intravenously. Although the test showed no free complement in the blood, these animals reacted typically when reinjected with the protein used for sensitization. Nor do the interesting salt experiments of Friedberger, where the intravenous injection of 1 c.c. of saturated sodium chlorid solution prevents the anaphylactic reaction in the guinea pig, demonstrate the necessity of the complement, although strong salt solutions do inhibit the fixation of complement and antibody, as Ehrlich has shown. It might be assumed, for example, that the salt inhibited the activity, but not the formation, of the substance which produces the anaphylactic reaction, a supposition which was strengthened when Ritz showed that salt solutions exhibited a similar protective action against peptone intoxication. The change in osmotic pressure, moreover, produced by the salt leads to dilution of the blood, and this might be a factor (Bornstein). The true reason was advanced by Dale, who demonstrated with the excised uterus of sensitized guinea pigs as test object, that a small increase of tonicity from 0.9 per cent to 1.1 per cent in a solution bathing the preparation was sufficient to cause a strong reduction in the response of this muscle when the anaphylactic test was made. A rise in the concentration of the bath solution to 1.3 per cent produced almost complete abolition of response to the antigen. That a much greater concentration is at least momentarily obtained by the injection of 1 c.c. of a saturated salt solution in a small guinea pig is clear, and Dale calculates that this amount raises the sodium chlorid content of the blood, at least momentarily, to 3 per cent.

From the experiments quoted above it seems that the complement is not an essential factor in the anaphylactic reaction.

Changes in the Blood Picture.—During the anaphylactic reaction in the dog the leukocytes show a diminution in number. The leukopenia is due to a practical disappearance of the polymorphonuclear cells from the circulating blood, while the mononuclear forms and the blood-platelets show an increase. As the animal recovers the polymorphous forms gradually increase and a leukocytosis develops (Biedl and Kraus). Leukopenia occurs also in the rabbit and guinea pig. This specific leukopenia was observed first during the serum disease and investigated by von Pirquet and Schick, who state that the number of leukocytes increases moderately during the period of incubation, but then sinks considerably during the appearance of the serum reaction. Here also the leukopenia is due almost entirely to the diminution in polymorphonuclear cells; the mononuclear forms show a slight relative increase. Von Pirquet and Schick call attention to the fact that the leukocyte curve during serum disease shows a strong resemblance to that observed in measles, small-pox, and vaccinia.

Leukopenia may be produced in rabbits by a single injection of horse serum (von Pirquet and Schick). The eosinophilic cells are not increased during the acute reaction in experimental anaphylaxis of the guinea pig and dog, but occur in considerable numbers after a delayed reaction. In addition to peripheral eosinophilia, Schlecht and Schwenker obtained marked eosinophilia of the lung tissue and bronchi in guinea pig, and the inflammatory edema of the subcutaneous tissue (Arthus' phenomenon) showed the exudate cells to be largely true eosinophils. Eosinophils in large numbers were also found in the submucosa of the gut of dogs who succumbed eleven to eighteen hours after reinjection.

This eosinophilia is apparently a true anaphylactic reaction, for Schlecht and Schwenker obtained no eosinophilia of the lungs after a single intraperitoneal injection of serum; nor did a single inhalation of sprayed serum lead to local eosinophilia of the lungs, but inhalation of serum by a sensitized pig caused typical eosinophilic infiltration of the lung tissue. Asphyxia or the intraperitoneal injection of Witte's peptone did not affect the eosinophils. There is no relation between the degree of anaphylactic reaction and the degree of eosinophilia. In passive anaphylaxis no eosinophilia is observed.

Huber and Koessler state that eosinophilia is an important symptom of human bronchial asthma and furnishes evidence of sensitization with an antigenic protein or of an intoxication with higher peptones. These authors consider eosinophilia the chief cellular symptom of the allergic reaction in man.

Lymph.—Lymph of the dog, collected from the thoracic duct, is greatly increased in quantity during the anaphylactic reaction; at the same time the lymph, like the blood, becomes incoagulable (Calvary).

In the plasma and serum of guinea pigs which died in the anaphylactic reaction H. and L. Hirschfeld demonstrated vasoconstricting substances when perfused through the Trendelenburg frog preparation. These men are inclined to consider the substances protein cleavage products.

Nervous System.—Although the nervous system formerly occupied a prominent place, especially in theoretical discussions of anaphylaxis, the number of demonstrable functional or anatomical lesions is not great. Gay and Southard observed occasional hemorrhages in the brain, medulla, and spinal cord of guinea pigs. The same authors also described lesions of the peripheral medullated sensory and motor nerves stained by the Marchi method; these were focal in type, in the myelin sheath, and especially noticeable at the node of Ranvier. The same authors noted an increased irritability of the vagus nerve in guinea pigs sensitized with horse serum when horse serum was applied to that nerve; this increased irritability was said to show itself by marked respiratory symptoms; the application of physiological saline had no effect.

Yamanouchi, on the other hand, describes a reduction of sensitiveness when the cut sciatic nerves of rabbits sensitized with horse or bovine serum were bathed with the serum used for sensitization. The loss of irritability or conductivity (Yamanouchi does not state whether the faradic stimuli were applied at or above the site of the serum application) occurred within one minute after the cotton soaked in serum was applied. The reduction was marked: before the serum application, when only saline had been applied, 340 mm. coil distance gave a response; after the serum application a coil distance of 190 mm. was necessary. This loss, moreover, was specific; application of horse serum to the nerve of a rabbit sensitized with bovine serum, and vice versa, had no effect.

The observations of Fröhlich may perhaps furnish the anatomical basis for Yamanouchi's results, although Fröhlich worked with frogs. The frogs had been sensitized by the injection of sheep or pig serum into a dorsal lymph sac. After eight to fifteen days they were curarized and the mesentery prepared for microscopical examination in vivo. Local application of the serum used for sensitization caused a marked local edema of the non-medullated nerve fibers in the mesentery, so that the nerves were often three times as thick as normal. This damage to the nerve was only observed in the neighborhood of the site of application; further away the nerves always showed a normal outline.

Temperature Changes.—In the subacute anaphylactic reaction the temperature sinks markedly, and in very mild cases this lowering of the temperature may be the only manifestation that an anaphylactic reaction has occurred. In acutely fatal reactions in the guinea pig different animals behave differently and no drop in temperature may occur. Pfeiffer, who discovered this "temperature drop," soon realized that the abrupt lowering of the temperature is not characteristic when considered by itself alone, for a large variety of substances may produce the same effect. By a strict adherence to a certain dosage, weight of the guinea pig, and so forth, Pfeiffer, however, believes that a drop in temperature of more than 1.5° C. is conclusive evidence that an anaphylactic reaction has taken place.

In order to gain some insight into the causation of the drop of temperature the respiratory gaseous exchange has been examined. Both Scott and Loening observed in rabbits and guinea pigs placed in a respiratory chamber that a non-fatal anaphylactic reaction causes a diminution in the carbon dioxid output and in the oxygen consumption. Loening suggests that there is no increased dissipation of heat, but a definite diminution of heat production, for measures taken to prevent the loss of heat of the animal did not affect the result.

The temperature drop of Pfeiffer, which has also been observed in the rabbit and dog, is not the only temperature change which occurs in sensitized animals. Friedberger and his collaborators, especially Mita, observed that the temperature drop in sensitized guinea pigs becomes less with a decrease in the dose employed for reinjection, and finally with a certain dose no temperature effects are obtained. If, however, this non-effective dose is still further decreased so that they are infinitesimal, Friedberger and Mita then observed rises in temperature. In normal guinea pigs the injection of a foreign protein, as is well known, also causes fever, but Friedberger and Mita show that the quantity necessary for this effect is many thousands of times less in sensitized guinea pigs than in normal ones. The sera employed by Friedberger and Mita were horse and sheep sera, which were used as fresh as possible both for sensitization and re-injection. By a judicious variation in the amount of foreign protein injected, and in the interval between injections, Friedberger produced continuous, remittent, or intermittent fever in sensitized guinea pigs. This protein fever he explains as the result of protein cleavage products which are formed by the body from the injected protein; this digestive capacity which the normal organism possesses is enormously increased in the sensitized organism because specific antibodies are present which facilitate the formation of these pyrogenic components from the protein molecule.

Vaughan also has independently produced in animals all the various types of fever which are met clinically by the injection of a toxic protein fraction. Both he and Friedberger give highly suggestive and stimulating applications of these facts in regard to the temperature reactions of the acute infectious diseases.

Local Anaphylaxis.—Local reactions occur in the sensitized organism when the foreign protein is injected intracutaneously, subcutaneously or into the conjunctiva or trachea. The ophthalmo-reaction of Wolff-Eisner and Calmette, and the skin reaction of von Pirquet for tuberculosis probably belong to this class. The marked local reaction known as Arthus' phenomenon serves as the type reaction and has been described briefly on page 96. It may be added that Schlecht and Schwenker found the infiltrated cells of this local reaction to be largely eosinophiles. The effects obtained by local applications of the antigen to arteries and nerves (Fröhlich, Yamanouchi, Gay and Southard) have already been described.

When sensitized guinea pigs are allowed to inhale a fine spray of the foreign protein Friedberger obtained pneumonialike changes in the lung. Ishioka, with the same procedure, obtained only slight lung changes, but observed definite lesions when the foreign serum was injected into the trachea. The quantities injected were very small, 0.05 to 0.1 c.c. The majority of the guinea pigs showed genuine pneumonias when killed. The pneumonia was lobar in type, though a whole lobe was rarely involved; the bronchi were not inflamed and the alveoli contained leukocytes, fibrin, and red corpuscles. All the lungs examined showed a more or less pronounced emphysema, which Ishioka considers an important factor in the production of the pneumonia.

Local anaphylactic manifestations may also be called forth by means of conditions which Auer has described as an auto-inoculation. This author observed that sensitized rabbits reinjected with a non-fatal dose of the antigen developed dry gangrene of the ear, if xylol was applied to this structure shortly after the reinjection. The dose of xylol employed caused a temporary inflammatory edema, but no gangrene, in the ears of normal rabbits, sensitized rabbits or normal rabbits injected with antigen shortly before the xylol application. Auer attributes this striking effect to a local, anaphylactic reaction: the amount of antigen circulating in the reinjected animal is not sufficient to call forth a noticeable reaction in non-inflamed cells, but it is sufficient to do this in irritated, inflamed cells because their metabolism per unit of time is greater than the metabolism of non-inflamed cells; for this reason a subliminal concentration of the antigen for non-inflamed, sensitized cells, may pass beyond the threshold value when inflamed, sensitized cells are concerned, and an anaphylactic reaction becomes observable. Such a process may occur in any tissue capable of showing an anaphylactic response. Auer suggests that this mechanism may perhaps explain a number of functional abnormalities in the human subject, and perhaps some of the drug idiosyncrasies may find an explanation in this enchainment of conditions.

It is possible also that the same process of auto-inoculation may be a factor in determining the degree of sensitization which is achieved; irritated, inflamed cells will absorb a greater amount of the antigen and, therefore, become more highly sensitized than non-inflamed cells. That the amount of the antigen injected plays a part in the degree of sensitization obtained has already been shown.

CENTRAL OR PERIPHERAL CAUSATION OF THE ANAPHYLACTIC REACTION

In the preceding description of some of the main alterations which the anaphylactic reaction produces in the various animal species, enough evidence has been given to show that in many instances these alterations are clearly of peripheral origin and are not dependent upon a reaction occurring in the cells of the central nervous system. Nevertheless, as the central nervous system was not absolutely excluded, and as reactions in the nerve cell were formerly prominent in the explanation of anaphylactic phenomena, some of the experiments which definitely excluded the central nervous system may now be briefly reviewed.

Pearce and Eisenbrey proved that the brain and medulla of the dog had nothing to do with the anaphylactic drop of blood-pressure by obliterating all vascular connections between the head and trunk of a sensitized dog and maintaining an independent circulation through the head and neck by transfusion from the carotid artery of a normal animal. Under these conditions the injection of a foreign protein (horse serum) into the independent cerebral circulation of the sensitized animal caused only a slight, transient lowering of the blood-pressure. When, however, the serum was injected into the trunk a typical persistent drop of blood-pressure took place.

This fine experiment of Pearce and Eisenbrey shows absolutely that the centers of the medulla and brain, especially the central vasomotor mechanism, have no part in producing the drop in blood-pressure. The same authors also demonstrated that after destruction of the cord and section of the vagosympathetic nerves a drop of blood-pressure, nevertheless, results when the animal is reinjected. For the dog, therefore, it has been definitely established that the medulla and brain exert no causative effect upon the anaphylactic drop in blood-pressure.

That the typical anaphylactic lung in the guinea pig is due to peripheral causes, and is entirely independent of the central nervous system, was shown by Auer and Lewis and by Schürer and Strasman, who obtained the typical response after section of the vagi and destruction of the brain, medulla, and spinal cord. A still more striking proof was furnished by Schultz and by Dale, who produced the typical reactions in isolated organs.

The cardiac changes which are found in the anaphylactic reaction in the rabbit were obtained by Auer after section of the vagi and destruction of the cord, medulla, and basal brain; cardiac anaphylaxis was described by Launoy in the excised heart of sensitized guinea pigs after perfusion with the antigen; and Coca demonstrated, physiologically, contraction of the pulmonary arterial circuit after death of the rabbit on perfusion with the antigen. For these anaphylactic alterations the central nervous system is again not necessary.

The local anaphylactic reactions typified by Arthus' phenomenon are probably also produced independently of the central nervous system, though this has not yet been proved; it is difficult at least to conceive how the central nervous system could be the chief factor in this disturbance.

It must be observed that the experiments where the central nervous system was destroyed, or where the typical reaction was obtained with the excised organ, only show that the brain, medulla, and cord are not necessary to obtain the typical result; they do not justify the inference that no reaction occurs in the central nervous axis. Rigid evidence for such a statement has so far been furnished only for the blood-pressure drop in the dog, where the higher nervous centers were maintained in a state of integrity by a cross circulation from a normal animal (Pearce and Eisenbrey).

There is no definite evidence that the higher nervous centers are primarily affected in the anaphylactic reaction. The initial respiratory changes observable in the rabbit which sometimes occur before the blood-pressure declines are perhaps due to a central effect. The initial rise in blood-pressure in the same animal may perhaps also be caused by a stimulation of the vasomotor center. The respiratory symptoms in the dog and guinea pig, however, are probably not due to a primary effect upon the nervous centers. In the dog they are best explained by an anemia of the higher centers which is secondary to the drop in blood-pressure, and this also accounts for the stage of excitation and the following depression. The respiratory symptoms in the guinea pig from beginning to end are very likely secondary to the asphyxia which begins as soon as the protein is reinjected intravenously.

The rise in temperature, nausea, and vomiting may possibly be due to primary central effects.

The diarrhea in dogs is probably largely peripheral and is caused by the congestion of the mucosa, the increased secretion of the pancreas, and especially by the strong contractions of the intestinal musculature.

Besredka's experiments on the protective action of ether anesthesia in the anaphylactic reaction of the guinea pig do not demonstrate a central action of the anaphylactic reaction because ether causes a bronchodilatation, as Dixon and Brodie have shown, and this bronchodilatation probably neutralizes or reduces the bronchoconstrictor effect of the reinjection. Morphin, chloral-hydrate, and urethan also probably owe their effect to the same action on the bronchial tubes.

As another proof that the higher nerve centers are the seat of anaphylactic reactions Besredka and Steinhardt advanced the great sensitiveness of sensitized guinea pigs to intracerebral injections. This, however, is no rigid proof, for the results following such an injection may just as well be due to rapid absorption, as the brain is richly supplied with blood-vessels.

The protective action which trephining exerts on the guinea pig, according to Friedberger and Gröber, is difficult to explain, unless vascular shock and consequent poor absorption were produced by the operation.

It is therefore seen that the central nervous system on the whole seems to occupy a surprisingly subsidiary place as far as primary anaphylactic changes are concerned. That a large number of secondary reactions occur in the brain and medulla as the result of peripheral anaphylactic changes is, of course, obvious.

ANAPHYLACTIC MANIFESTATIONS IN MAN

Serum Disease.[5]—The best known example of anaphylaxis in man is the symptom-complex called serum disease by von Pirquet and Schick. In a classical research these authors investigated the functional disturbances which occur in a percentage of cases after single or repeated injections of therapeutic sera in the human subject. Serum disease is characterized by fever, skin eruptions, swelling of the lymph glands, edema, leukopenia, and joint symptoms. The general condition, as a rule, is excellent.

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[5] Serum disease may still be chosen as an example of anaphylaxis, though Coca logically excludes it as a symptom-complex where no unequivocal evidence has yet been furnished that it really is an antigen-antibody reaction.

The onset of the symptoms does not occur at once after the first injection in the great majority of cases, but only after a quite definite period of incubation, usually eight to twelve days. The amount and character of the serum apparently exert no effect on the duration of incubation; nor is the incubation period referable to a delayed absorption for the antitoxic effects of the sera injected are exerted a few hours after injection. Moreover, quantities as large as 200 c.c. of serum leave no definite swelling twenty-four to forty-eight hours after a subcutaneous injection.

After the period of incubation fever and skin eruptions develop. The fever is one of the most constant symptoms, and may last from a few days to several weeks. It may be of a continuous or remittent type, and may reach 104° F. and over. The quantity of serum injected bears a definite relationship to the incidence of serum disease: after small amounts of serum, not more than 15 c.c., about 6 per cent showed fever; but after the injection of 100 to 200 c.c., 85 per cent of the cases showed the serum disease.

The skin eruptions present a great variety of forms and are mostly closely associated with the fever; they may be urticarial, scarlatinoid, morbillous, or polymorphous exanthems. Usually the first exanthem which appears belongs to the urticarial group. The first crop lasts a short time, but new ones may appear in other places for days. The exanthems usually appear first at the site of injection; the succeeding ones generally affect symmetrical parts of the body. The exanthems, like the fever, may last from a few days to several weeks.

Preceding the appearance of the eruptions the lymph glands draining the site of injection often become enlarged and tender. The enlargement increases and becomes general as soon as fever and skin eruptions develop. The glandular swelling decreases shortly before the general serum disease process abates, and is therefore of prognostic value.

During the incubation period the number of leukocytes is moderately increased, but an abrupt diminution takes place on the appearance of serum manifestations. The leukopenia, which is almost entirely due to a diminution of the polymorphonuclear type, lasts only a few days, and then disappears abruptly.

Joint symptoms are quite infrequent, but are very painful when present. They occur chiefly in the metacarpophalangeal, the wrist, and knee joints, but examination reveals no objective alterations. Von Pirquet and Schick never observed any permanent disability as a result of these joint symptoms. For treatment the authors advise cooling lotions; the administration of salicylic acid preparations gave no relief.

Edema may be a pronounced symptom during the serum disease; its location is similar to the edema of nephritic origin, first the face, then the dependent parts of the body. As a rule there are no symptoms of kidney irritation, and the albuminuria, when it does occur, never exceeds 0.25 per cent. This albuminuria, when present, is noted first during the second and third week, and not immediately after the serum injection. The edema persists throughout the course of the serum disease, but begins to decrease shortly before the end of the disease. This decrease in edema has the same prognostic value as the decrease in swelling of the lymph glands; both indicate that the end of the serum disease is at hand. Von Pirquet and Schick consider this edema as a primary symptom, and not as a secondary effect of kidney congestion or insufficiency.

The mucous membranes are only exceptionally involved during the serum disease, but in a number of cases a diffuse bronchitis and bloody diarrhea were observed. A causal relationship between these disturbances and serum disease von Pirquet and Schick consider probable only for the diarrhea. It will be remembered that diarrhea is a prominent feature in the anaphylactic reaction of the dog.

Reinjections.—If a patient has been once subjected to the action of a therapeutic serum, especially if large amounts were incorporated, his reaction to a subsequent injection varies in a definite way.

1. After an interval of twelve to forty days an immediate reaction occurs which may be local or general, or both. Within twenty-four hours after the injection the local swelling increases markedly in size, and urticaria and fever appear; the symptoms last only one to two days as a rule, but may be quite severe. There is practically no incubation period. It is hardly necessary to point out that the local edema following the injection corresponds to Arthus' phenomenon in the rabbit.
2. After an interval of one and one-half to six months an immediate and an accelerated reaction may occur. The accelerated reaction is one where the incubation period is shortened to five to seven days. The symptoms are the same as those observed after a first injection: fever, exanthems, edema, etc. The accelerated reaction may also last only a single day, but, like the immediate reaction, may be quite severe.
3. After an interval of more than six months only the accelerated reaction is observed as a rule.

The time intervals given above for the appearance of immediate and accelerated reactions must not be taken in a rigid sense, as many variations occur. Goodale, for example, observed an immediate (after thirty minutes) and an accelerated reaction (after four days) in a case which was reinjected subcutaneously seven years after the administration of the first dose. On first injection this individual showed serum disease after an incubation period of eighteen days. Goodale's case also illustrates the length of time that sensitization may be maintained in man.

The immediate reaction, local, as well as general, is sometimes obtained on first injection, but von Pirquet and Schick consider the accelerated reaction as practically pathognomonic of the fact that the patient has been treated previously with serum. Von Bókay, however, observed a case where comparatively fresh serum (two months old) produced an accelerated reaction in a child which was injected for the first time.

The frequency with which the serum disease occurs depends largely upon the amount of serum injected. Formerly, when 100 to 200 c.c. were injected, von Pirquet and Schick observed the serum disease in 85 per cent of the cases. With the reduction in quantity necessary to administer the proper amount of antitoxic units to 5 to 15 c.c. the percentage sank to about 6. This diminution has also been observed in the reinjected cases. Nemmser collected nine hundred cases which had been injected twice, and one hundred and two cases which had received three to five serum injections, nevertheless, only forty-two (4 per cent) developed a serum exanthem. Still more interesting was Nemmser's observation that not one of these one thousand and two reinjected cases developed serious anaphylactic reactions.

An observation of von Bókay seems to show that the character of the serum may play a rôle in the frequency with which serum exanthemata develop. In 1908 von Bókay noted that 19 out of 183 cases (10 per cent) developed the serum disease, but in 1909 the number increased to 23.5 per cent (43 out of 184). All the 1909 injections had been made with the serum from one horse, and von Bókay concludes that the increased occurrence of serum disease was ascribable to some individual peculiarity of the horse which furnished all the serum.

Other Anaphylactic Manifestations in Man.—Serum disease, as characterized by the immediate and accelerated reactions in man, is not the only anaphylactic effect observable in man. Cases of collapse, and even death, have been reported after the injections of small quantities of serum, though these accidents fortunately are rare. The symptoms observable under these conditions bear some resemblance to those observed in the lower animals, and it is probable that their causation is the same. A few examples may be given to illustrate this. Von Pirquet and Schick report a case which was reinjected with 16 c.c. of serum twenty-seven days after the first injection. Within ten minutes the site of injection showed redness and urticaria; a short time later urticarial patches appeared scattered over the body. Fifteen to twenty minutes after the injection the boy began to vomit, his eyes rolled inward, the extremities became cyanotic, salivation occurred, and the pulse was no longer palpable. After the application of stimulants and warm packs the boy recovered.

This case probably suffered from a severe drop in blood-pressure, which was caused by a paralysis of the vasomotor endings of the gut, similar to that obtained in the anaphylactic dog, or by a weakening of the heart such as occurs in an anaphylactic rabbit, or by a combination of these two factors.

The first injection of horse serum has been followed in a number of instances by collapse and death, with symptoms which are very suggestive of those which occur in the dog, rabbit, and guinea pig. Gillette has collected a number of cases from the literature where the injection of antidiphtheria serum caused collapse and death under symptoms which suggest the picture of acute serum anaphylaxis in the guinea pig and rabbit. In this collection of 30 cases 22 gave a previous history of respiratory trouble, especially asthma. On injection some of them showed a remarkable dyspnea, and even convulsions, while the pulse remained full and regular. A picture of this type resembles the anaphylactic reaction in the guinea pig. Moreover, in 2 cases the lungs were apparently larger than normal on autopsy. In other cases the injection produced a feeling of anxiety, depression, cyanosis, and complete collapse, associated with a feeble pulse. Cases of this type undoubtedly indicate disturbances of the heart and circulation, such as may be observed in the rabbit and dog during the anaphylactic reaction.

Disturbances of the gastro-intestinal canal have already been mentioned; von Pirquet and Schick reported 2 cases in their monograph, and Gottstein called attention to a hemorrhagic enteritis which was observed a number of times on autopsy.

Reactions after Intraspinal Injections of Serum.—Especially severe and sometimes fatal cases have been reported after intraspinal injections of antimeningitis serum, and these reactions have often been ascribed to anaphylaxis. Although anaphylactic reactions can easily be obtained from the spinal canal, as Besredka and Lissofsky have shown in the guinea pig, nevertheless a study of some of the human cases, which are frequently quoted as examples in the literature even by Besredka, does not bring conviction that they are undoubtedly anaphylactic. To illustrate this statement the well-known report of Hutinel may be mentioned.

The paper of Hutinel, for example, reports 4 cases of death after the intraspinal injection of the Dopter antimeningitis serum, and protocols are given of 3. Two of the cases died after an intraspinal injection of 30 c.c. given after intervals of three and five days. The intraspinal injections before this were given daily. The arrangement in time of the injections does not suggest that a high degree of sensitization could be produced. The incubation period is exceedingly short, only a few days; moreover, the daily injections ought to have produced the so-called immunity which is obtained in guinea pigs by the daily administration of massive doses of serum. In the third case, 150 c.c. of serum was injected in toto, 40 of them subcutaneously; serum disease developed after seventeen days and lasted eight days. Another intraspinal injection of 20 c.c. was administered forty-four days after the last one, but only a general urticaria without fever developed in three hours and disappeared in twenty-four (immediate reaction of von Pirquet and Schick). But another intraspinal injection of 30 c.c. given only five days after the last one caused death. Here again the period of incubation is too short for a high degree of sensitiveness; moreover, the patient should still have been more or less refractory from the previous injection. The doubt that anaphylaxis is the cause of death is strengthened still more by the clinical symptoms and the speed with which they developed. All developed symptoms shortly or immediately after the injection which are observable after a rapid rise in intracranial pressure: hyperextension of the body, with or without convulsions, and subsequent coma. Immediate responses were also observed by Besredka when serum was injected intraspinally in guinea pigs, while the anaphylactic symptoms appeared only one to five minutes after the injection. In Hutinel's Case 3 the symptoms are described more closely: the respiration was extremely slow and irregular; the inspiration slow and noisy, the expirations short and followed by long pauses. Pupillary and corneal reflexes were abolished; the face was cold and pale; the extremities cyanotic. As the symptoms persisted lumbar puncture was performed after five minutes and 30 c.c. withdrawn "with ease." The respiration improved at once; the face gained color, but the coma persisted and the patient died after one and one-half hours. The temperature remained normal.

In this last case also the symptoms were at least partly due to cerebral pressure. In all these cases it appears unlikely that anaphylaxis caused the symptoms; they were probably due to an increased pressure in the central nervous system, a supposition which is strengthened by the fact that the serum was apparently injected without first withdrawing an equal bulk of spinal fluid.

The case reported by Grysez and Dupuich probably belongs to the same category. A patient received intraspinally 100 c.c. of Dopter and Flexner serum given in six injections during eight days. After twenty-three days another injection was necessary. In order to avoid anaphylaxis the authors injected 2 c.c. of Flexner serum intraspinally and waited three hours for desensitization to establish itself. Then 40 c.c. of Flexner serum was injected. After 30 c.c. was in, the head was retracted violently and fibrillary contractions appeared; the patient was semicomatose with stertorous respiration, dilated pupils, cyanotic face, and thready pulse. Nevertheless the injection was completed. The patient recovered swiftly as from a sleep, state the authors.

In these cases of Hutinel and Grysez and Dupuich the dominant rôle attributed to anaphylaxis in the production of the symptoms is therefore at least open to question, and they should not be cited as undoubted proof. While intraspinal injections of serum undoubtedly may produce anaphylactic reactions, the frequency of severe anaphylactic effects has probably been overestimated, and they can under no condition be considered a contra-indication to the therapeutic use of the serum.

Food Idiosyncrasies.—There are numerous cases on record where the ingestion of certain protein foods, such as eggs, pork, milk, and sea food in general, produced marked reactions. At least some of these cases are true examples of anaphylaxis, for passive sensitization of guinea pigs has been accomplished with the sera of some of these patients. These idiosyncrasies may be so marked that, for example, the application of egg-white on the skin or mucous membranes may produce a severe reaction. Sensitization in these cases was probably accomplished through an abnormally permeable respiratory or gastro-intestinal mucosa, or the tendency may have been inherited. The same explanation probably applies to those cases which react severely to the first injection of horse serum, and here also inhalation, ingestion, or heredity may explain the sensitized state.

Hay Fever.—This disease is probably also an example of anaphylaxis, and is caused by the proteins of various pollens. The disease does not develop before the fifth year, and may not occur until adult age. It is therefore probably acquired, and its acquisition is apparently aided by an abnormal permeability of the nasal and intestinal mucosæ.

PASSIVE ANAPHYLAXIS

The injection of an animal with a foreign protein is not the only way in which sensitization can be produced. The sensitized state may also be established by injecting into a normal animal the blood or serum of an animal already sensitized. This important fact that the sensitized state is transferable from one animal to another was discovered by Gay and Southard and by Otto for foreign serum, and by Richet for toxalbumins. In active anaphylaxis, therefore, a reaction body or antibody is formed which carries the property of sensitizing against that protein to which it owes existence. Because a reaction body is formed in active sensitization the proteins which produce anaphylaxis are often called anaphylactogens, thus classing the anaphylactic reaction with the other well-known immunity reactions.

The transfer of the sensitized state may be obtained, not only between animals of the same species (homologous sensitization), but also between those of different species (heterologous sensitization), provided that the animals employed are mammals, for the attempts passively to sensitize mammals from fowl, or vice versa, have failed. The animal employed most frequently for the production of the anaphylactic reaction body is the rabbit, and the test is usually made in the guinea pig, because this animal is more readily passively sensitized than the rabbit or dog.

A refractory period is always present in the guinea pig when the antiserum is injected first. After intraperitoneal injection in the guinea pig a twenty-four-hour interval is necessary, but this period is shortened to four hours when the antiserum is injected intravenously. Reactions are, however, obtained in the guinea pig when antiserum-antigen mixtures are injected intravenously. Since the refractory period is always present when the two components are injected separately, it is quite possible that the reaction obtained with the mixture is not one of passive anaphylaxis, but is perhaps due to the formation of a poison by the interaction of antigen and antiserum; this supposition is strengthened by the observations that the simultaneous, but separate, injection of antiserum and antigen (each into a jugular vein), or the injection immediately after the mixture, as a rule, produces no reaction.

The necessity of the interval between the injection of antibody and antigen is explained by the assumption that the antibody undergoes certain changes in the guinea pig or enters into certain relations with organs before it is able to react with the antigen and produce the disease.

Conditions are somewhat different in passive anaphylaxis of the rabbit, for here no interval is necessary between the injection of antibody and antigen; the animal is immediately sensitized after the injection of the antiserum, and reacts even more powerfully when the antigen is injected at once than if a twenty-four-hour interval is allowed to elapse. Moreover, it has been shown that a specific local edema may be obtained in the rabbit when the antigen is injected first and the antiserum after twenty-four hours; in the guinea pig this procedure prevents passive sensitization.

The symptoms produced when passively sensitized animals are injected with the appropriate antigen are identical with those obtained during active anaphylaxis, and experimental analysis has established the same alterations in passive as in active anaphylaxis.

The anaphylactic reaction body has not been demonstrated in the blood of guinea pigs before the animal itself has been sensitized by the foreign protein. Nor can it be detected in the blood during, and for some time after, the anaphylactic reaction. It has, however, been obtained later in the antianaphylactic stage, and may produce passive sensitization while the animal furnishing the antibody is still refractory to another injection of the antigen.

It is interesting to note that free antibodies cannot be detected in the blood after a certain time, although the animal is still sensitized. This is probably to be explained by the assumption that the antibodies remain sessile and do not leave the cells forming them.

The length of time passive sensitization persists is only a few weeks; a test made after fifteen days is, as a rule, negative.

Much time and labor has been spent in the endeavor to identify the anaphylactic reaction body with precipitin, but the outcome has not been a decisive answer for or against this view. Longcope has recently stated, however, that, in the white rat, sensitization and precipitin formation are entirely independent of each other, for horse serum failed to sensitize this species of animal but produced, nevertheless, precipitins in fairly high concentrations. Longcope used all the ordinary methods employed to sensitize and reinject the test animal; as criteria for the shock reaction he used the symptoms produced by histamin and peptone injections. Experiments on the uterus of virgin rats treated vigorously with preparatory injections of horse serum and tests for skin sensitiveness also gave negative results. Though Longcope's results are clean-cut yet it must be kept in mind that the absence of the ordinary signs of an anaphylactic reaction does not necessarily mean that no anaphylactic reactions occurred. It is conceivable that the anaphylactic reaction in the white rat, as well as in the monkey, may be quite different from that observed in the other laboratory animals where involuntary muscle changes dominate the picture.

Passive sensitization can also be studied in the excised organ. Dale has demonstrated that the uterus of a normal guinea pig, when perfused for five hours with a 20 per cent solution of antihorse serum from guinea pigs, followed by a perfusion of 500 c.c. Ringer solution, gave a typical tetanus when bathed in a 0.2 per cent solution of horse serum. After relaxation and thorough washing of the organ with Ringer solution the renewed application of horse serum had no effect; the uterus was antianaphylactic. Dale was also able to resensitize the uterus of an actively sensitized guinea pig after the preparation had once responded and was demonstrably antianaphylactic. In this case mere bathing, not perfusion, for three hours in a 10 per cent solution of sensitive guinea pig serum was sufficient to restore sensitization, and the preparation now responded typically when normal horse serum was added to the bath solution. As mere bathing in the antibody did not sensitize a normal uterus, Dale suggests that the cells which have once held antibodies take them up again more readily than normal muscle cells.

ANTIANAPHYLAXIS

After a sensitized animal has recovered from the anaphylactic reaction it becomes refractory to another injection of the same protein. This refractory state was first observed by Otto and by Rosenau and Anderson; Besredka and Steinhardt named this state antianaphylaxis. A relatively short time only is necessary to bring on this refractory state, and its length depends upon the method chosen for the incorporation of the protein: after intraperitoneal injection one to two hours are necessary; after intravenous injection the desensitization occurs almost immediately; the longest time interval is necessary after subcutaneous injection. This rapid development of antianaphylaxis renders it possible to give large amounts of the antigen to a sensitive animal without producing symptoms, provided that the antigen is injected repeatedly in small amounts (Besredka), or is infused intravenously at very slow speed (Friedberger and Mita). While Friedberger and Mita's procedure protected as a rule only against ten fatal doses (time consumed during the injection was fifty to sixty minutes), Besredka has been able to protect against more than two hundred fatal doses of the antigen. The procedure of Besredka is as follows: In actively or passively sensitized guinea pigs, where the fatal dose is known, a fraction of this dose is injected subcutaneously, intraperitoneally, or intravenously. This dose vaccinates against one or two fatal doses within four hours if the vaccinating dose was administered subcutaneously, or within five minutes if the vaccination was intravenous. Repeated injections of this type gradually raise the tolerance to a high level. For example, in guinea pigs sensitized with egg-albumin 1/500 c.c. intravenously killed in four minutes. In one animal of this series 1/2,000 c.c. was injected intravenously with no reaction; after ten minutes 1/500 c.c., the fatal dose, was injected with no effect; aften ten more minutes 1/50 c.c. was tolerated perfectly; ten minutes later 1/5 c.c. (one hundred fatal doses) caused no reaction; somewhat later 2 c.c. of undiluted egg-albumin was injected into the jugular vein. This injection of one thousand fatal doses gave symptoms, but the animal recovered rapidly.

On the basis of these results Besredka does not hesitate to give explicit directions to the physician how to proceed when it is necessary to inject serum intraspinally in order to avoid anaphylactic complications, for Besredka mentions 10 cases of death which he attributes entirely to anaphylaxis.

Antianaphylaxis occurs in the rabbit, dog, and doubtless in man, as well as in the guinea pig, although differences exist between the species. The duration of the antianaphylactic state is very short in the rabbit, and lasts only a few days (Scott). Guinea pigs, however, which have been injected intraperitoneally repeatedly with large doses of protein may remain antianaphylactic for long periods of time, although their blood shows the presence of antibodies. Rosenau and Anderson have produced an antianaphylaxis in this way which lasted for months. This procedure has been called an immunization by some authors, but it has been shown by Weil that it is really a state of latent hypersensitiveness. Weil proved that the so-called immune guinea pigs prepared by massive injections are really hypersensitive, and will succumb provided that a sufficiently large dose of the antigen is injected intravenously. Their refractoriness, according to Weil, is due to the fact that the sessile antibodies of the body cells are protected by the large amount of circulating antibodies.

Other important facts regarding the production of antianaphylaxis were contributed by the same author. Weil showed experimentally that guinea pigs sensitized with fractional doses of antigen can be desensitized or rendered antianaphylactic with small doses, while, after sensitization with large doses, large amounts of antigen are necessary to accomplish this purpose. The reason is that the number of antibodies formed stands apparently in some relation to the amount of antigen used for sensitization: after fractional doses the amount is small; after large doses the amount of antibodies present is much greater. Experimentally, therefore, unless the fatal dose or size of the sensitizing dose is known, antianaphylaxis can only be produced by a slow process of graded doses such as Besredka employs, without any knowledge of when the desensitization is complete. This is a point of great importance in the practical application of Besredka's methods in the human subject, and Weil is justified in warning not to expect in man the striking results Besredka obtained in guinea pigs.

Neutralization of the anaphylactic antibody is not the only method of producing a refractory state. It may also be established by the injection of a number of other substances, for example, Witte peptone, as Biedl and Kraus have shown in the dog. If a dog, sensitized with horse serum, is injected with peptone, the dog, after recovery from this injection, does not react to a horse serum injection; it is thus in an antianaphylactic state. This non-specific antianaphylaxis, however, is not of high degree, nor does it last a long time. The differentiation between non-specific and specific antianaphylaxis has been especially investigated by Friedberger and his collaborators.

Antianaphylaxis can also be obtained in the excised organ, as Launoy has shown for the guinea pig's heart, and Dale for the excised guinea pig's uterus.

Desensitization may also occur locally. Mackenzie and Baldwin describe a series of cases suffering from cutaneous hypersensitiveness which could be abolished by the repeated cutaneous or intracutaneous application of the substance to which the individual was sensitive. This loss of reactivity was apparently specific and lasted up to three days. With histamin, on the other hand, Sollman could demonstrate no refractory state of the skin. Mackenzie and Baldwin employed egg-white, horse serum, extracts of ragweed and chicken-feather and also proteins from almond, pea, oat and wheat in their study.

PREVENTION OF ANAPHYLACTIC REACTION

Lower Animals.—The best procedure is perhaps Besredka's method of desensitization by a series of graded doses of antigen, and his procedure has been described in the section on Antianaphylaxis. In addition to this method a number of different substances may be mentioned whose administration has abolished, reduced, or prevented the characteristic reactions in the animals used for the experimental investigation of anaphylaxis.

Sodium Chlorid.—Friedberger and Hartoch have protected guinea pigs by injecting about 1 c.c. of a saturated sodium chlorid solution intravenously before the antigen was given. The protective action is probably due to a reduced irritability of the smooth muscles which the increased tonicity of the blood causes (Dale).

Barium Chlorid.—Biedl and Kraus raised the blood-pressure in the anaphylactic dog by the intravenous injection of 50 to 100 mg. of barium chlorid. A previous injection of the salt even prevented all anaphylactic symptoms in a sensitized dog.

Peptone.—Biedl and Kraus observed that sensitized dogs, after recovery from the peptone shock (approximately 0.25 to 0.5 gm. per kg. intravenously), are immune to a subsequent injection of the antigen. Trypsin and foreign proteins, excluding those used for sensitization, also produce a temporary, non-specific reduction of anaphylactic reactions.

Ether Narcosis.—Besredka recommended this procedure, and obtained good results in guinea pigs. The protective action, which is not great according to other observers, seems to be entirely due to a reduction in irritability of the bronchial muscles. In dogs vomiting is abolished by ether narcosis, but the characteristic drop in blood-pressure occurs promptly, with no sign of any diminution.

Atropin.—This alkaloid was recommended for use in the guinea pig, because it is the direct antagonist of the death-producing effect exerted in acute anaphylaxis in this animal, for atropin relaxes the bronchial muscles. The dose is 1 to 5 mg. intravenously, depending upon the severity of the reaction. A prophylactic dose of 2 to 10 mg. may be given subcutaneously. The protection is not absolute, but against a minimal lethal dose it protects in 70 per cent of the cases (Auer). It is only indicated in respiratory effects of the asthmatic type.

Urethan and Adrenalin.—Both of these substances have a relaxing effect upon the bronchial muscles, as Dixon and Brodie showed for urethan, and Januschke and Pollak for adrenalin. Anderson and Schultz were able to save 66 per cent of their guinea pigs by combining these two drugs with chloral hydrate and giving artificial respiration with oxygen gas.

Chloral Hydrate.—The action of chloral hydrate was investigated especially by Banzhaf and Famulener. These authors saved 75 per cent of highly sensitized guinea pigs by injecting about 75 mg. of a chloral hydrate solution (10 per cent) intramuscularly twenty to thirty minutes before the intraperitoneal incorporation of the foreign protein (horse serum). This dose given is for a 250-gm. guinea pig. The drug may also be administered by intracardial injection: 30 mg. per 275 to 300 gm. of weight, repeated after two to four minutes. This procedure protected

75 per cent of the sensitized animals from an intracardiac injection of the horse serum.

Man.—Before discussing the methods which are available for the production or treatment of severe anaphylactic reactions in man a few general remarks are necessary. It has already been shown that, while reactions do occur, they are not common, and their frequency can be decreased if certain precautions are observed.

No therapeutic serum or vaccine should be administered without stringent indications for its use. It is well always to keep in mind that a foreign, undenatured protein calls forth not only specific but also an unknown number of non-specific alterations in the reactivity of the body, and the consequences of these changes are not invariably assets to the treated organism. The joyous abandon with which these powerful and imperfectly subdued drugs are being employed will also be curbed by remembering that the subtle changes induced by an alien protein may persist for months and even years.

The serum should not be fresh. Fresh serum is in itself toxic. According to Boehncke, it would appear that the reluctance of physicians to inject older sera is not well founded. Boehncke found no diminution in the antitoxic value of diphtheria antitoxin aged for ten years, provided that the serum was protected from light and heat. Even when kept at a temperature of 37° C. for five months the serum showed only a slight loss.

A purified serum should be used when possible. The diminution in the amount of serum proteins necessary to produce results, for example with diphtheria antitoxin, has decreased the appearance of serum disease considerably.

Intravenous injections of therapeutic sera should only be given when the patient's condition absolutely demands it. As a routine practice it is undoubtedly more dangerous than the subcutaneous injection, for laboratory experience has shown conclusively that highly sensitized guinea pigs easily recover from a subcutaneous dose, a fraction of which would kill if given intravenously. It must be noted, however, that Park has observed about 300 cases where 5 to 7 c.c. of antitoxic serum was injected once or repeatedly without any serious symptoms. After larger intravenous injections of antistreptococcic serum (100 to 200 c.c.) the same observer noted a serious collapse but once in a sensitized case.

Caution must be exercised when it becomes necessary to administer a therapeutic serum to patients who have chronic respiratory troubles, especially asthma, or who have been injected previously with horse serum. With asthma cases desensitization ought to be attempted according to Besredka's methods.

In subjects who have already been injected with horse serum the danger is apparently not so great, though severe reactions do occur (Netter, Darling, and others). Nemmser collected the histories of 1,002 cases, of which 900 had received two injections, and 102 three to five injections of diphtheritic antitoxin and failed to find any record of a severe anaphylactic reaction. Moreover, fever and exanthems developed only in 42 patients. The results are probably partly due to the small dose of serum employed, which varied between 6 to 10 c.c. for each injection.

When therapeutic sera are injected intraspinally (antimeningitis serum) a bulk of spinal fluid equal to the amount of serum to be injected should first be removed. It is more than probable that at least some of the cases reported by various observers, where convulsions and collapse occurred immediately after the injection, were due to pressure rather than to anaphylaxis. In experienced hands, moreover, the occurrence of severe symptoms is quite rare (Park).

Though all the dangers incident to the warranted exhibition of therapeutic sera are usually negligible in comparison to the dangers of the untreated disease, yet it will do no harm if the physician keeps in mind that the untamed protein molecule of a therapeutic serum or vaccine is the bearer, not only of desirable, but also of undesirable gifts.

Besredka's Methods.—Besredka has described the following procedures especially for intraspinal injections of sera, when the patient has been sensitized by previous administrations of serum; in practice, however, he advises that every patient be considered as possibly sensitized.

If the diagnosis of intraspinal meningitis is undoubted 2 c.c. of the serum is injected intraspinally. After at least two hours the final dose of 20 to 30 c.c. is injected.

If the case is very urgent then the intravenous method of desensitization is recommended, 1 c.c. of a 10 per cent solution of serum being injected intravenously; after four minutes 3 c.c. more; ten minutes later 10 c.c. are injected; after two more minutes 25 c.c. of the dilution are infused. Four minutes later the patient is desensitized, according to Besredka, and is able to endure 10 to 30 c.c. of undiluted serum either intravenously or intraspinally.

If the diagnosis of meningitis is doubtful Besredka advises, nevertheless, to inject the enormous dose of 10 to 20 c.c. of serum subcutaneously for vaccinating purposes, so that the next day the patient may, if necessary, receive 20 to 25 c.c. intraspinally.

It seems quite certain that these vaccinating doses advised by Besredka for the human being are too large. Netter noted collapse after a subcutaneous vaccinating injection of 2 c.c. serum in a child which had been injected twice before, the intervals being twenty-nine and fourteen days, and Netter in consequence recommends that much smaller quantities be used for vaccinating purposes, for example, 0.1 to 0.01 c.c. This procedure would surely be safer, and its efficacy has been demonstrated in the guinea pig. In this connection the warning of Weil should be remembered, that a safe desensitizing dose can only be determined when the minimal lethal dose is known; a fraction of this dose could then be used with certainty as the first dose in the desensitization process. The minimum lethal dose is, of course, never known in the human subject, and this fact is therefore another strong argument for starting the vaccination process with extremely small quantities.

After severe anaphylactic symptoms have set in the treatment is more or less symptomatic. If the respiratory symptoms are of an asthmatic type atropin is indicated to relax the bronchial muscles. Adrenalin also relaxes the bronchial muscles (Januschke and Pollak), and besides delays absorption (Meltzer and Auer), thus facilitating desensitization.

If the blood-pressure is low adrenalin may be given, although Biedl's and Kraus' results in the dog were not encouraging. Barium chlorid is very toxic, but perhaps could be employed cautiously in cases of extreme and persistent low blood-pressure. Biedl and Kraus obtained gratifying results in anaphylactic dogs with this drug.

For cardiac weakness and failure, which possibly also occur in the severe types of anaphylactic reaction in man, no treatment has been described. Digitalis preparations, if employed, must be used with caution, for Auer has observed that they apparently hasten cardiac death in the anaphylactic rabbit.

The treatment of serum disease is preventive and symptomatic. The prophylactic treatment is to use as small a quantity of serum as possible, and this has diminished the incidence of serum disease after antidiphtheritic serum considerably. The symptomatic treatment, according to von Pirquet and Schick, is as follows:

Urticaria: 1 to 2 per cent salicylic acid or 1 per cent menthol in alcohol, or 1 per cent menthol salve.

Fever: wet packs; no antipyretics.

Arthritis: salicylic acid preparations were found useless; baths and local applications.

Diarrhea: attention to diet and the ordinary treatment. Edema and albuminuria cannot be prevented by any known means.

CRITERIA OF ANAPHYLAXIS

The diagnosis of experimental anaphylaxis should not be made unless at least Conditions 1 and 2 are fulfilled.

1. The animal must have been sensitized by an alien protein. After an incubation period the reinjection of the same protein must produce a reaction or reactions which are not obtained, or not to the same degree,

when the same amount of the same protein is injected in the same way into normal, non-proteinized animals.

2. After recovery from this anaphylactic reaction or reactions, a refractory state for at least some of these reactions should be demonstrable when the same protein is again incorporated in the same way, employing the same dosage used to elicit the anaphylactic reactions.
3. It is desirable that passive sensitization be positive.

It will be observed from the description of the anaphylactic reaction in the dog, rabbit, and guinea pig that there is no single sign which appears with equal intensity in the three species: for example, the lung immobilization is found practically only in the guinea pig, and even there only after acute death; it does not occur in the rabbit, and only exceptionally in the dog; the characteristic abrupt drop in blood-pressure is observed only in the dog, and the drop observable in rabbits and guinea pigs has generally a different character; the coagulability of the blood may be lost in the dog, strongly reduced in the rabbit, and only slightly decreased in the guinea pig; vomiting is common in the dog, but does not occur at all in the rabbit or guinea pig; and so on, through all the symptoms or signs ever described in experimental anaphylaxis. This varying intensity of effect of the anaphylactic reaction upon the different systems of organs in the dog, rabbit, and guinea pig must be clearly kept in mind, for in anaphylaxis, as in every other reaction studied in vivo, each animal species must be measured with its own yardstick. At least some of the confusion in the literature of anaphylaxis is directly traceable to failure to realize this. The main factor which caused this error was the desire to unify, to standardize one anaphylactic reaction for all species of animals.

It must also be remembered that none of the functional and anatomical changes which occur during the anaphylactic reaction in any animal is by itself alone diagnostic of an anaphylactic reaction. All these changes, which have been described in some detail in the preceding pages, do not permit the diagnosis of anaphylaxis, unless they have been obtained on reinjection of some foreign protein. In other words, the functional and anatomical changes themselves are not characteristic of anaphylaxis, but the procedure of obtaining them is characteristic. What this procedure is has been described; the animal must first be sensitized by the incorporation of a foreign protein; after a period of incubation the reincorporation of the same protein must produce symptoms which were not present when the animal was first injected, or at least were not present to the same degree. This procedure is the essence of the symptom-complex of anaphylaxis, and only by its recognition were Theobald Smith, Otto, and Rosenau and Anderson enabled to differentiate it from similar intoxications caused by other means.

The anatomical and functional changes which the different animal species, especially the guinea pig, present during the anaphylactic reaction may be produced to some extent by a large variety of different substances, many of which are of non-protein nature. For example, toxic normal sera; immune sera; fresh defibrinated blood; urines from normal, anaphylactic, or scalded animals; protein cleavage products; products of putrefaction; bacterial and pollen extracts; saponin; potassium cyanid; copper sulphate, colloidal iron, colloidal arsenic; collargol, arsphenamine, neoarsphenamin, sodium arsenate, citrate and oxalate, venarsen; agar, gelatin, althea, acacia, tragacanth, dextrose, inulin, glycogen, starch; kaolin; and many other substances may give a clinical and anatomical picture, when injected into guinea pigs, which resembles that obtained on reinjection of a foreign protein in a sensitized animal. Since so many different substances produce an apparent similar result, it is clear that great caution is necessary as soon as any one of them is indicated as the cause of experimental anaphylaxis, for it is obvious that this statement can only be an inference based on identity of action. That this inference is not justified is clearly shown when one considers that an identity of functional response to various causes proves by no means that these various causes are identical; although saponin and Witte peptone may produce practically the same lung picture in the guinea pig, it cannot be concluded from this observation that saponin and Witte peptone are identical chemically, though they may be functionally identical in certain reactions. Similarly, a symptomatology resembling that of true anaphylaxis, produced for example by histamin, does not prove that histamin is the active agent in true anaphylaxis. It may be added that the symptoms produced by histamin are classed as anaphylactoid by Hanzlik and Karsner.

In order to differentiate between those substances which produce changes similar to, or perhaps even identical with those obtained after the reinjection of a sensitized animal, Auer and Loewit have suggested that the term "anaphylactoid" be applied to the alterations resembling the anaphylactic types of reaction, but which are obtained on first injection into a normal non-sensitized animal.

Some of the anaphylactoid phenomena demand further consideration.

ANAPHYLACTOID PHENOMENA

It has already been pointed out that a large number of chemically different substances, when injected into an organism, produce at once symptoms which resemble those noted during the anaphylactic reaction. Such substances are found among the cleavage products of proteins, and have been investigated especially by Vaughan, Schittenhelm and Weichardt, Biedl and Kraus, and many others. The important researches of

Vaughan showed that all proteins can be split into a toxic and a non-toxic constituent by boiling for several hours in a 2 per cent solution of sodium hydrate in absolute alcohol. The toxic portion is alcohol soluble, the non-toxic fraction is insoluble. With the toxic fraction Vaughan and his collaborators were able to produce on first injection in guinea pigs the symptoms and anatomical signs which are observable in the anaphylactic reaction of this animal. When injected into dogs Edmunds observed in general the same symptoms which acute anaphylaxis calls forth in this animal. The toxic fraction does not sensitize, but the non-toxic moiety can sensitize against the whole protein molecule, but not against itself.

Schittenhelm and his collaborators examined the protein cleavage products separately, and demonstrated that a number of different poisons are formed which individually often show certain resemblances in their physiological effect to the anaphylactic reaction; they observed a drop in blood-pressure, leukopenia, diminished coagulability, and, in the guinea pig, an immobilization of the lung.

Biedl and Kraus injected Witte's peptone into dogs and guinea pigs, and obtained in both animals effects which they considered identical with those observed in true anaphylaxis in these animals. They conclude that the anaphylactic intoxication is caused by a poison which is to be considered physiologically identical with the active constituent of Witte's peptone. It must be remembered that Witte's peptone is an exceedingly complex mixture of substances, and that its composition varies apparently in different samples. One must agree, therefore, with Wells that results obtained with this variable commixture are of doubtful value.

In a large series of papers Friedberger and his collaborators have attempted to prove that a toxic mixture produced in vitro by the action of fresh guinea-pig serum upon specific precipitates (immune serum and antigen) is the true anaphylactic poison, because it produces the typical symptoms when injected into normal guinea pigs, and because this toxic material, or "anaphylatoxin," is formed from the same constituents whose interaction in the body apparently causes the anaphylactic intoxication. It is impossible here to survey the enormous literature which Friedberger's anaphylatoxin has called forth, and for an adequate critical presentation of this question the reader must be referred to the general review of Doerr. In general it may be said that Friedberger's anaphylatoxin theory is a modified form of the protein cleavage theory, for the "anaphylatoxin" is said to be split from the antigen by a process of digestion in which the complement and immune body play essential rôles.

A large number of substances, which on first injection produce symptoms in the guinea pig resembling those of true anaphylaxis, have been experimentally investigated by Hanzlik and Karsner. These authors on the basis of careful and painstaking investigations protest against carelessly identifying the disturbances produced by various agents after intravenous injection with those observed in true anaphylaxis. Their series of papers is the most exhaustive analysis of anaphylactoid phenomena at present available.

Among the anaphylactoid phenomena the so-called drug idiosyncrasies must also be placed, at least for the present. No definite evidence has yet been advanced that crystalloid substances produce the formation of an antibody of the type of the anaphylactic reaction body. It is possible that some of the drug idiosyncrasies may be explained on the basis of Auer's theory of auto-inoculation (page 139). For the large literature on this subject see the recent reviews by Doerr and by Coca.

THEORIES OF ANAPHYLAXIS

As soon as the striking phenomena of anaphylaxis were carefully investigated a number of theories were devised to explain their causation. A detailed consideration of these theories is beyond the scope of this article, and only a brief consideration of the leading conception will be given.

Many investigators consider the symptoms of anaphylaxis as due to an intoxication, to a poisoning of the tissue cells. This poison was thought to be formed either by the union of the antibody and antigen alone, or this combination of antibody-antigen was activated by the complement, and now, by a process of parenteral digestion, toxic cleavage products were formed from the antigen which produced the symptoms of anaphylaxis. This conception of an etiological relationship between anaphylaxis and protein cleavage products is the leading one at the present time, although, as Doerr points out in his excellent review, the most intensive work has not so far been able to establish the following three fundamental points: (1) the determination of the mother substance whose cleavage furnishes the poison; it is not known whether the injected antigen or the body proteins, or both, furnish these hypothetical cleavage products (Zunz); (2) the structure and properties of this poison, or poisons; (3) the proof that these products are formed during the acute anaphylactic reaction; the anaphylactic lung of the guinea pig, for example, where these cleavage products must be present, according to hypothesis, showed no increase in the content of albumoses, peptones, or amino-acids, as determined by the method of Van Slyke (Auer and Van Slyke). Obviously these objections do not invalidate the parenteral digestion theory of anaphylaxis; it still remains the most attractive explanation yet devised, nevertheless the existence of these objections must be clearly kept in mind, for they show that the theory is by no means firmly established.

The parenteral digestion theory of anaphylaxis was first formulated on the basis of clean-cut experiments by Vaughan, and his exposition and development of it by laboratory work has enriched our knowledge with many important facts and aided the comprehension of confusing phenomena. Vaughan's theory is briefly as follows: The introduction of a foreign protein into the tissues or circulating juices of an animal develops in that animal a proteolytic ferment which is specific for the protein injected. This specific ferment remains in the cells of the animal as a zymogen, and is activated when the same protein is again injected. A sensitized animal is thus one whose cells are rich in a specific proteolytic zymogen; moreover, each foreign protein has its predilection tissue, where it is largely deposited, whose cells it especially sensitizes, and where it is disrupted. As all proteins are conceived to be composed of a toxic and a non-toxic fraction, and as the second injection of the foreign protein activates the specific zymogen, the active ferment is liberated, splits the foreign protein, and the freed toxic component now produces the symptoms of anaphylaxis. The first injection of the foreign protein produces no toxic symptoms, because there is no specific ferment present, and the non-specific ferments present split the foreign protein so slowly that at no one time is a sufficient amount of poison liberated to produce the ordinary symptoms of anaphylaxis.

Antianaphylaxis, according to Vaughan, is due largely to the quantitative disproportion between the small amount of specific ferment now available and the foreign protein; for the anaphylactic reaction uses up a large part of the ferment, and the remainder can produce too little poison to exert any effect. Passive anaphylaxis is explained as the transfer of the specific proteolytic zymogen, the antibody in terms of Ehrlich's theory, from a sensitized animal to a normal one.

This is the bare skeleton of Vaughan's theory, a conception which, in various forms, has been more fruitful of results than any other theory of anaphylaxis formulated thus far. Whether time will demonstrate its truth or not matters little; it has already fulfilled the main function of a theory: it has stimulated research and produced an abundance of new facts.

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CHAPTER V

FOCAL INFECTION IN RELATION TO SYSTEMIC DISEASE

FRANK BILLINGS

The principle of the development of a systemic or localized disease from a previously existing infectious focus is a long-established fact.

Rheumatic fever, endocarditis, generalized tuberculosis, gonorrheal arthritis, and septicopyemia are familiar examples. Not only acute, but chronic systemic, disease, including cardiovascular and visceral degenerations, may be caused by a chronic focal infection. Chronic focal infection may exist for a long period without apparent harmful result; the defenses of the body probably prevent general infection.

It is also true that an insidious slow systemic intoxication may occur from a focal infection which is finally recognized because of disturbed function of various organs. Myocardial degeneration, chronic nephritis, and arterial fibrosis are the most common expression of the slow, insidious intoxication. Of course, other factors—inheritance, a bad personal hygiene, food and drink abuses, occupation, etc.—may play the more important part in these degenerative processes; but exclusive of these recognized etiologic factors, chronic focal infection may be the cause of cardiovascular and kidney and other disease. The focal infection may disappear spontaneously and coincidentally, the evolution of the systemic disease may cease, leaving the patient more or less an invalid, or entire recovery may occur. This is witnessed in individuals suffering from chronic arthritis, myocarditis, and even in moderate grades of nephritic disease.

SITE OF THE FOCUS

The focus, acute or chronic, may occur anywhere in the body. Usually the focus is located in the head, probably because the mouth and air passages are so frequently exposed to infection. Bacteria-laden air, insanitary dwellings, faulty individual mouth hygiene, etc., play an important part. In childhood the lymphoid tissue of the nose and throat may be excessive and apparently affords a favorable soil for infection. The faucial tonsil and adenoid overgrowth in the nasopharynx are the frequent seats of infection. Obstructed infected crypts of the tonsil due to chronic tonsillitis or to the sealing scar of tonsillotomy are a common focal source of many systemic diseases. Dental alveolar infection, especially chronic abscess, curiously often unperceived by the patient, is a frequent source of general debility and chronic arthritis. Modern dentistry, characterized by wonderful technical skill in the use of gold crowns and bridgework, is sometimes the cause of the alveolar focus of infection.

Chronic infection of the various sinuses of the head, especially if undrained mucopus exists, may cause systemic disease.

Infection may pass from the throat and sinuses along other mucous tracts and involve the eyes and also the middle ear and mastoid cells, or it may pass through the lymphatics to the meninges or to the lymph glands of the neck. The lymph glands so infected may form additional foci of danger to systemic disease. The genito-urinary infections are frequent sources of general disease. Gonorrheal septicopyemia and arthritis are examples. Urinary stasis from prostatic enlargement, stenosis of ureters, foreign bodies, etc., are usually associated with colon, streptococcus, Bacillus pyocyaneus, or other bacterial infection, and may be the causes of systemic disease.

Cholecystitis and cholangitis may cause bacteriemia and degenerative changes in the heart, blood-vessels, and kidneys. Chronic appendicitis may be a cause of local distress and a danger to life through abscess formation with rupture and resulting septic peritonitis. Quite as dangerous to health and life may be the resulting degenerative changes of myocardium, arteries, kidneys, and other organs of surgically neglected chronic appendicitis. Local septic foci of the submucous and subcutaneous tissues anywhere may cause systemic disease. Septic venous thrombi due to infection of contiguous tissues are sources of septicemia.

The intestinal tract may be the source of invasion of bacteria, as in typhoid fever, cholera and dysentery, as water or food-borne infections. These general diseases do not fall under the principles of this article.

Much has been written of the chronic, local, and systemic disease due to the intestinal bacteria. Probably under abnormal anatomical conditions of the tract, with stasis of intestinal contents and sluggish blood circulation, ordinarily innocent bacteria (colon and streptococcus intestinalis) may acquire pathogenic virulent properties with resulting local and systemic disturbances of various organs. Unusual intestinal bacteria (B. aerogenes capsulatus, B. proteus vulgaris, Streptococcus viridans, and Streptococcus pyogenes) may have an etiologic relation to pernicious anemia, chronic arthritis, cardiovascular and visceral degenerations. The mesenteric lymph-nodes may become infected with bacteria from swallowed mucopus derived from primary foci located in the mouth, the throat or accessory nasal sinuses, but the infection of the lymph-node is more likely to occur from primary foci located in the mucous membrane of the intestines. The infected mesenteric lymph-nodes may continue to be a source of systemic infection after the eradication or spontaneous disappearance of the primary foci. Complete colonectomy has been performed for chronic arthritis, for types of psychosis, upon the theory that the causative infectious agents have their source in primary infection of the mucous membrane of the colon and secondary foci in the lymph-nodes.

SYSTEMIC DISEASES OF FOCAL ORIGIN

The systemic diseases which may be focal in origin may be divided into the *acute* and *chronic* forms.

Of the acute diseases rheumatic fever, malignant endocarditis, simple endocarditis, streptococcemia, staphylococcemia, gonococcal septicopyemia, and arthritis are familiar typical examples. The chronic systemic diseases of focal origin are chronic arthritis (streptococcus and gonococcus), myositis, neuritis, myocarditis, nephritis, arteriocapillary fibrosis, and degenerative processes in various viscera.

The focus of systemic infection may apparently give rise in one individual to an acute process, and in another to a chronic disease. This is especially true of the acute and chronic forms of arthritis, myositis, and endocarditis and appears to be due to the modification which the streptococci, the usual cause, may undergo in known mutation of cultural characteristics and pathogenicity in varying culture media and serial animal inoculations (Rosenow). Clinical observations and coincident bacterial experimentation apparently prove this statement. Strains of streptococci (Streptococcus *viridans, mucosus, hemolyticus* and *rheumaticus*) have been obtained by cultural methods from infected crypts and abscesses of tonsils, dental alveoli, and other foci; from the exudate of sinusitis; from joint exudates in acute and chronic arthritis; from excised muscle in chronic myositis; from the blood in malignant and simple endocarditis; from the fibroid nodes upon the sheaths of tendons and aponeurosis of muscles in arthritic patients, and finally from enlarged lymph-nodes near the infected joints and have been made to change their cultural characteristics and to vary in pathogenicity by changing the culture media, the oxygen tension and by serial animal passage.

It seems rational to make the deduction that mutation of specific pathogenicity may take place in the streptococcus-pneumococcus group in the focus of infection. Acute streptococcic tonsillitis may occur immediately before or during rheumatic fever. Often there is a history of one or more attacks of "sore-throat" in previous weeks, months, or years. The same story is of common occurrence in the more chronic arthritic, muscular, and myocardial diseases. The streptococci in the latent focus may change in specific pathogenic character because of some biochemical qualities of the tissue in which they lie. Probably the local blood supply and the oxygen content of the locally infected tissue play an important part in the mutation.

With the defenses of the body diminished by overwork, dissipation, exposure to cold, insufficient or improper food; by unhygienic surroundings; by injuries from previous disease (valvular scar), or trauma (joint or muscle), the individual may suffer from acute or chronic arthritis, myositis, or malignant or simple endocarditis or pneumonia, dependent upon the phase of mutation in pathogenicity of the specific strain of the streptococcus-pneumococcus group in the local focus.

Relation of Suspected Focus to Systemic Disease.—The relation of a suspected focus to the systemic disease seems to be proved in many instances by several factors. The removal of the infected focus by surgical or other means is sometimes followed by rapid recovery from the systemic disease. Many observers have noted the great improvement in the general health by tonsillectomy, removal of postnasal adenoids, drainage of a chronically infected gall-bladder, appendectomy in chronic appendicitis, and removal of carious teeth and alveolar dental infection. One must recognize the improvement in the ability to breathe when obstruction of the air passages is relieved by tonsillectomy and removal of adenoids; a better digestive power and consequent improved nutrition by correction of dental faults, relief of local distress in cholecystitis and appendicitis, but, admitting this, it seems obvious that relief from continued systemic infection is the chief reason for the general improvement.

PATHOLOGY OF CHRONIC SYSTEMIC INFECTION OF FOCAL ORIGIN

The streptococci in the focus of infection apparently attain specific pathogenic qualities (see above) with affinity for joint tissues, kidneys, muscles, including myocardium, gastro-intestinal mucosa, gall-bladder, endocardium, lung, etc., respectively.

The specific streptococci pass through the blood-stream and lodge in the arterioles and capillaries of the organ or tissues as embolic masses. Small hemorrhages result in heart valves, muscles, mucosa of stomach and gall-bladder, kidney, etc. (Rosenow). As a result of the embolism and hemorrhages, characteristic changes occur in the infected tissues and elsewhere in the body. Rosenow has shown in experimental animals hemorrhages, subsequent ulceration, and characteristic massive vegetations with contained thrombi of the heart valves after the intravenous injection of a strain of Streptococcus viridans obtained from the blood of a patient ill with subacute Streptococcus viridans endocarditis; hemorrhages and subsequent leukocytic infiltration and degeneration of voluntary muscles and myocardium; hemorrhage into and subsequent ulceration of the mucous membrane of the stomach and intestine; hemorrhage into and subsequent infection of the gall-bladder; hemorrhage of the glomeruli of the kidneys with hematuria, cylindruria, albuminuria, after the intravenous injection of various strains of streptococci. Similar pathological processes have been obtained in the clinical and pathologic studies of patients suffering from malignant endocarditis, myositis, cholecystitis, ulcer of stomach, hemorrhagic nephritis, etc. Cultures of the specific cocci have been obtained from the lesions named in both animals and patients.

Additional pathologic changes occur which are characteristic of the organ primarily or chiefly involved. The massive vegetations and contained thrombi serve as a rich culture medium for the specific streptococcus (Streptococcus viridans) in subacute Streptococcus viridans endocarditis, with consequent constancy of the streptococcemia. In the chronic type of the disease the defenses of the body (antibodies) apparently become exhausted; the infectious organism becomes immunized against the host (Welch). The streptococci are also disseminated throughout the body by means of the detached particles of vegetations and thrombi, which lodge as emboli in all the organs and tissues. This generalized embolism may produce constitutional disturbance and various local phenomena (petechiæ of skin, hematuria, splenomegalia with splenic tenderness and hemiplegia).

The infected voluntary muscle groups and their aponeuroses are tender, painful and contracted in the acute stage. In the chronic stage, painless when at rest, they are shortened by contraction from interstitial degeneration and thickening due to the infection, local anemia, and nonuse.

The small submucous gastric embolic hemorrhage is followed by anemic necrosis and subsequent digestion of dead tissues. The acute ulcer may bleed and imperil life or a typical chronic peptic ulcer may be the final result.

In the gall-bladder the embolic focus and hemorrhage are usually located at the base, the situation of the terminal blood-vessels. The rupture of this submucous focus into the gall-bladder may cause cholecystitis and gall-stones also may form. Hematogenous embolic infection of the soft tissues of the joints occurs in experimental inoculation of animals. Similar embolic hemorrhages occur in the capsule, the synovial sac and fringes and bones in man and animals.

The changes which occur in the cartilage, bones, and other joint structures in chronic deforming arthritis are illuminated by the experiments of Oxhausen. The simple aseptic necrosis of bone and cartilage resembling the morbid anatomy of atrophic and also hypertrophic types of arthritis deformans was produced by cutting off the blood supply of the joint, with resulting anemia of joint structures. Injuries of joints resulting in diminished blood supply have been known to produce a like morbid anatomy of the joint. It may be that the anemia plus the toxins of embolic joint infection will explain the hitherto unknown metabolic changes of chronic arthritis. The general malnutrition and anemia so commonly present in this class of patients would be an additional factor

RESULTS OF SECONDARY FOCI OF INFECTION

The secondary foci in the various organs and tissues are capable in some instances of intensifying the systemic disease. Mention has been made of the growth of bacteria in the thrombi-containing vegetations on the heart valves in malignant endocarditis. The condition furnishes a constant bacterial multiplication which is added to the blood-stream. The usual infectious organism in this type of endocarditis is the Streptococcus viridans. The peculiarity of this organism is that it has only moderate virulence as compared with many other strains of streptococci. One of its peculiarities is that it requires a high oxygen tension for its growth, and this it finds as a surface growth in focal infection and in the blood-stream in malignant endocarditis. Probably it is this peculiarity of this type of streptococcus, and the fact that the thrombic vegetations which it produces on the heart valves act as a good cultural medium for it, that make this disease so fatal. It finds on the heart valves a good secondary focus where it may grow, and it finds a rich oxygen content in the blood-stream.

Infected lymph-nodes proximal to the focus of infection may become secondary foci. General tuberculosis, acute and deforming rheumatism, endocarditis, simple and malignant, and other systemic disease may develop from the secondary foci.

The embolic foci of the systemic disease are found in muscles and other tissues, and have been shown by Jackson to occur in the terminal blood-vessels of the tissues of joints. The fact that the infection occurs in an embolic form, including many blood-vessels, and thereby reducing the blood supply of the infected organs, explains many of the peculiarities of the chronic types of myositis and arthritis. The injury to the blood-vessels partially deprives tissues of blood, and thereby interferes with their nutrition and oxygen supply. The types of streptococci which infect muscles and cause chronic arthritis have also a low virulence. They grow best in a low oxygen tension. The fact that the embolic process deprives the tissues of blood and lowers the oxygen content furnishes the best possible conditions for continued viability and probably also for multiplication of the infectious microörganism. This peculiarity of the pathology of the chronic types of myositis and arthritis also explains the progressive morbid anatomy so peculiar to these diseases. The metabolic changes which occur in the muscles and also in the bones and cartilages of the joints seem to depend upon the deprivation of the structures of those elements necessary for their general nutrition. Therefore, in the treatment which will restore the condition it is necessary that the nutritional side of the tissue be considered, attempts being made to restore circulation and full oxygen content to the tissue before the infectious microörganism can be destroyed and the morbid anatomical changes stopped. It explains the reasons for the improvement of patients who are managed along the lines of general support, including the improvement of the general nutrition of the body by good food, plenty of oxygen in the form of pure air, passive and active exercise commenced mildly and gradually increased, and all other measures which tend to build up the general health. One can also understand why patients so managed without a removal of the primary focus of infection may relapse because of reinfection. It explains why these patients are made definitely worse by all exhausting and depressing measures such as an insufficient diet with low proteid content; exhausting warm or hot baths and mental and physical fatigue.

FOCAL INFECTION AND ANAPHYLAXIS

The principles of anaphylaxis are especially and exhaustively explained elsewhere. The subject is mentioned here only to emphasize the fact that the body may be sensitized by the absorption of a protein substance from a focus of infection. This may result in periodic evidence of anphylaxis in the form of urticaria and other skin lesions, asthma, etc.

TREATMENT

Prophylaxis.—Focal infection is most commonly situated in the head, but may be located in any organ or tissue. The mouth and air passages are constantly exposed to infectious bacteria, especially in individuals who live in densely populated centers. Insanitary environment usually cannot be controlled. When possible this should be commanded. Individual hygiene should be enforced by municipal, county, and state health officers. This would be feasible in all public school children. The enforcement of a personal hygiene by public officers would educate and impress parents and other individuals with its importance. Enlarged or infected faucial tonsils, adenoid tissue overgrowth, and carious teeth are a menace to health and life. Tonsillectomy, thoroughly performed, may save the individual, especially a child, from local infection in the form of tonsillitis, peritonsillitis, diphtheria, etc., and also from consequent rheumatic fever, endocarditis, tuberculous lymphadenitis of the neck and mediastinum, nephritis, acute and chronic myositis, chronic deforming arthritis, etc.

Tonsillectomy should not be needlessly practiced, but when there is evidence that the tonsils are infected or enlarged by chronic disease they should be thoroughly enucleated to prevent further local and possible systemic disease. The function of the normal tonsil is not known. Its removal has not been followed by any recognizable local or constitutional disturbance. An infected or abnormal tonsil is a harmful organ and should be wholly removed. Partial removal (tonsillotomy) is a temporizing, dangerous measure. The remaining crypts, sealed over by the operation scar, afford a condition as bad or worse than the original tonsil.

Excessive adenoid tissue of the nose and pharynx prevents free drainage and obstructs the air passages. In addition to the local effects, the danger of middle ear, mastoid and lymph-gland infection, and possible systemic disease should indicate prompt operative correction.

Carious teeth are an inexcusable evidence of faulty personal cleanliness in those who are otherwise healthy. Constitutional conditions due to deficiency diet may be a cause of, or at any rate be associated with, caries and other diseases of the gums, teeth, and jaws. Caries of the teeth may lead to septic disease of the gums, to alveolar abscesses, etc. In children and others proper dentistry should be instituted to prevent focal disease, as well as the possible subsequent chronic arthritis, furunculosis and general debility. Modern dentistry has technical faults. The use of metal crowns upon teeth with infected pulp results, in many instances, in the establishment of mechanical dams over infectious foci.

Cholecystitis, especially if chronic, is a recognized cause of systemic disease, especially visceral degenerations. Myocardial degeneration is frequently associated with it. Improvement of the heart condition is often noted after cholecystotomy and drainage. Surgical treatment of cholecystitis and cholangitis is indicated, not only to relieve the local disease, but it is quite as important to prevent systemic slow intoxication and consequent myocardial and other visceral degeneration. Surgically neglected, appendicitis may be a local menace, may disturb the organs of digestion and in addition may cause systemic chronic intoxication and cardiovascular, kidney, and other organic degenerative changes. Neglected gonorrheal foci, located in the deep urethra, mucous glands of the prostate and in the seminal vesicles are dangerous in the dissemination of the disease in sexual intercourse and also of systemic infection of the host in the form of arthritis, tenosynovitis, gonococcemia with malignant endocarditis.

Septic conditions of the urinary tract, especially those due to defective drainage from pelvic disease of women and to morbid anatomical changes of the prostate, bladder, ureters, and kidneys, should receive appropriate surgical treatment and medical management to relieve local conditions and to prevent additional serious systemic disease.

Finally prevention of systemic disease from a focal infection should be promoted by all of the means which are known to maintain the natural defenses of the body, namely: pure air, simple good food, avoidance of overfatigue and exposure to extreme changes of temperature, especially that which lowers the temperature of the body for a relatively long period.

Methods.—The patient who suffers from acute or chronic arthritis, endocarditis, myositis, hemorrhagic and chronic nephritis, etc., should have repeated thorough physical examinations. Careful search should be made to locate the infectious focus. This is not always evident or easily found. That it is frequently present in the faucial tonsil should not lead to hasty tonsillectomy in all patients. Advantage should be taken of the Roentgen ray, of transillumination, and of the aid of throat and nose specialists in examination of the head. A complete history, careful physical exploration of the abdomen, test meals, fluoroscopic bismuth tests, microscopic chemical and bacterial cultures of stools may be necessary to recognize chronic foci in gall-bladder, appendix vermiformis, or elsewhere in the gastro-intestinal tract and of intestinal stasis with abnormal and pathogenic intestinal flora. Thorough investigations should be made of the genito-urinary tract by pelvic exploration and urine examination, chemical, microscopic, and, if necessary, by bacterial cultures. Massage of the prostate and seminal vesicles may yield the gonococcus and afford an immediate recognition of the cause and nature of the systemic disease. A denial of an acquired gonorrhea or the confession of an infection many years before should not excuse this examination in every male patient who suffers from arthritis.

Occasionally one will find the focal infection in an unusual place. A suppurating toe from an ingrowing nail has been the source of rheumatic fever with pancarditis in one patient, and of chronic deforming arthritis in another. Specific streptococci were obtained in pure culture from the pus under the toenail from both patients.

Removal of Focus of Infection.—When ascertained, the focus of infection should be eradicated by the necessary surgical aid or other means, which have been fully explained under Prophylactic Treatment. If accessible and not otherwise remediable, secondary foci in the form of enlarged lymph-nodes should also be surgically removed if there is a probability that they may continue to cause general infection as secondary foci.

In acute conditions like rheumatic fever, malignant endocarditis, and the like, it may be hazardous to attempt to remove the primary focus. It is questionable whether recognizably infected tonsils should be removed during the height of rheumatic fever. Inasmuch as many individuals are apt to have repeated attacks of acute rheumatism, the apparent focal cause (usually infected faucial tonsils) should be removed in the interval between attacks. In chronic types of infectious endocarditis it is wise to remove a recognized primary focus.

General Management.—The management of the patient after the removal of the focus of infection will, of course, depend upon the character of the systemic disease from which he suffers. Details of this management for each systemic disease cannot be suggested in an article of this kind. An attempt is made here to establish knowledge of the principles involved in the subject. The patient who suffers from malignant endocarditis must be treated in general as indicated in the literature which may be commanded. So, too, acute rheumatic fever, chronic deforming arthritis, gonorrheal arthritis, etc., must be managed as indicated in the numerous articles written upon those subjects.

Vaccines and Serum Treatment—*Vaccines.*—Vaccines have been used as specific methods of treatment in many of the systemic diseases due to focal infection. Autogenous vaccine has been extensively used in malignant endocarditis due to the Streptococcus viridans. Improvement by such vaccine has been reported, but it is the experience of the author that the use of vaccine in patients suffering from malignant streptococcal endocarditis is without benefit. Indeed, it seems that in some patients so treated by large doses, 500,000,000 to 1,000,000,000 of the autogenous vaccine, distinct harm resulted. Possibly small doses may increase the defenses of the body of the patient in this disease, but for the reasons stated in the paragraph on the pathology of the condition it is not likely that any remedy now known will affect the large vegetations upon the heart valves and produce antibodies in the blood-stream which will affect to any appreciable degree the life of the infectious organism. When Streptococcus viridans endocarditis is recognized early, before massive vegetations have formed, the intravenous injection of 5 to 10 gr. of cacodylate of soda in sterile normal salt solution, once a day or every second day, has resulted in permanently sterilizing the blood of a few patients ill with subacute endocarditis with positive blood cultures in the hospital service of the writer.

In acute rheumatic fever autogenous vaccine has not been sufficiently tried to enable one to make a definite statement concerning the value of the treatment. Stock vaccines so used have not produced good effects with regularity or uniformity, and the good results which have been reported are just as likely to have resulted from other influences, inasmuch as the natural clinical course is often changed by non-specific measures. The peculiarity of rheumatic fever in running a definite and limited course, as was shown by the elder Flint, makes all deductions concerning the use of remedies, whether drug or specific vaccines, a question which requires proof by the study of a large number of cases, properly controlled. The disease is not usually dangerous to life, so that the proof of the value of a "specific" remedy by the fact that 75 per cent or more of patients recover is begging the question. The fact that endocarditis, with resulting crippled heart valves, occurs in so many young patients who suffer from rheumatic fever is the important thing which should encourage one to seek for a method in the treatment of rheumatism which is specific. Until that time comes the wisest thing to do is to use prophylactic measures to prevent the disease and to follow well-known and established drug treatment and rational management.

The use of vaccines in chronic deforming arthritis and myositis has been practiced extensively (see Arthritis Deformans, Volume IV, Chapter XXI). It is the opinion of the author that, while autogenous vaccines may be specific to some degree in the treatment of chronic arthritis and myositis, the good result obtained in the management of these patients is due more largely to the improvement of the general health by the measures of general and individual hygiene which have been mentioned. Failure will occur in the management of this class of patients if reliance is placed wholly upon vaccines.

Serum.—In chronic arthritis and myositis a polyvalent streptococcus horse serum has been used. The serum was prepared by immunizing two horses with approximately thirty strains of streptococci of various types obtained from patients suffering from chronic arthritis and chronic myositis. The aged, refined, and heated serum was used coincidently with the autogenous vaccines. Under this management the defenses of the body seemed to improve more rapidly than with vaccines alone, as was manifested in a higher curve of both the opsonic and phagocytic index. Unfortunately the serum sensitized every individual upon whom it was used, and the use of the serum subsequent to the second or third dose produced more or less serum reaction (anaphylaxis). Usually this consisted of skin eruption—erythema and urticaria with intense itching—but in three patients the reaction amounted to a severe degree of anaphylactic shock and an alarming condition. Consequently the use of the serum was abandoned, as it was believed that the removal of the focus of infection followed by the general hygienic management mentioned, and the use of the less dangerous autogenous vaccines would be successful, without the serum. Autogenous colon vaccine has an unquestionable value in colon infections of the urinary tract (Billings). But to be successful there must be no stasis of urine in the tract. If there exist any morbid anatomical conditions (stricture of urethra, prostatic enlargement, stenosis of ureters from any cause, calculus or other foreign body in the tract, etc.) the infectious bacteria in the urine will persist until the cause of the stasis is surgically removed, and then vaccines will aid very much in rendering the urine sterile. If residual urine is associated with colon infection, daily bladder irrigation and the use of vaccines may give good results. However, as long as the cause of residual urine persists reinfection is apt to occur.

The use of what may be called polyvalent bacterial filtrates in any of the focal or systemic diseases mentioned in the subject of this paper is not justified by scientific experiments, rational deduction, or clinical results.

The use of vaccines and sera in gonococcal infections, asthma, furunculosis, and other diseases, focal and systemic, is discussed in the chapters relating to those subjects.

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CHAPTER VI

BACTERIAL SUBSTITUTION THERAPY

Arthur Isaac Kendall

LACTIC ACID THERAPY AND LACTIC ACID BACILLUS IMPLANTATION IN INTESTINAL TRACT

In this chapter on Bacterial Substitution Therapy particular attention has been given to lactic acid therapy and lactic acid bacillus implantation in the intestinal tract.

Early Studies.—The history of deliberate attempts to alter the flora of the intestinal tract begins with the studies of Metchnikoff. The theory underlying this type of therapy was foreshadowed in Herter's illuminating article which appeared several years earlier. The Metchnikoff theory centers around an assumption that auto-intoxication and premature senility are primarily attributable to overgrowth of putrefactive anaërobic microbes in the lower levels of the alimentary canal. The protean clinical manifestations resulting from this overgrowth are caused by the absorption of certain bacterial putrefactive products, which seem to act as cumulative poisons. The remedy for these conditions is to be sought for through the displacement of the putrefactive anaërobic bacteria. This may be brought about by the deliberate implantation of an intestinal flora, antagonistic to the anaërobes but harmless to the host.

Metchnikoff cast about for a suitable microbe to be implanted into the intestinal tract and selected the organism found in the casein balls used as starters for souring milk in Bulgaria. This bacillus, christened Bacillus bulgaricus, grows readily in milk *outside the body* and induces rapid coagulation therein, due to the relatively considerable amount of lactic acid it produces from the fermentation of the milk sugar.

The administration of milk soured with pure cultures of Bacillus bulgaricus was recommended by the originator of this method of therapy for cases of constipation, premature senility and for those presenting the somewhat intangible syndrome commonly referred to as "auto-intoxication." The underlying principle of Bulgarian bacillus therapy is very attractive, even to the layman, and it is not difficult to explain the wide use of soured milk prepared under Metchnikoff's general supervision. It should be recalled that he recommended the use of soured milk in conjunction with dietary changes designed to increase the effectiveness of the lactic acid regimen. These dietary changes are in brief a restriction of protein and a relative and absolute increase in the carbohydrate content of the food. Many times this dietary adjuvant to the soured milk was overlooked or disregarded. Many individuals prescribed Bulgarian milk for themselves. A not inconsiderable reason for disappointment in the outcome of a course of lactic acid therapy is doubtless attributable to neglect of these factors.

Making liberal allowance for these imperfections and even contra-indications, it must be candidly admitted that the results obtained with the use of Bulgarian milk have been less positive from a clinical standpoint than has been hoped for.

Some unexpected benefits have also been attained. Many persons who overindulged in proteins without regard for dietary balance and the actual food requirements for the body unconsciously followed the dietary principle of Metchnikoff's theory and benefited materially thereby. In some well-known clubs the sour-milk habit actually supplanted the cocktail habit. This was an unforeseen sequela. It is very probable that the consumption of soured milk has increased materially in the United States, even though a variety of microbes, naturally occurring and otherwise, produce the acidity of the medium. It seems unlikely that any material harm has resulted therefrom, and in the main sour milk has been popularized by Metchnikoff's labors and writings.

Turning now to the negative results of lactic acid therapy, which comprise for the most part actual cases where the Bulgarian regimen has been prescribed by the clinician, it appears justifiable to state that the percentage of positive, favorable results has been small in those patients where relief might be confidently expected. This applies more particularly to well-defined and somewhat advanced cases of auto-intoxication, where the absorption of intestinal putrefactive products is presumably taking place. Neither milk soured by Bacillus bulgaricus nor lactic acid itself seemed to have very favorable effect in many of these cases.

Recent Studies.—The decade and a half which has passed since Metchnikoff's studies appeared has been enriched with material advances in the knowledge of the chemistry and bacteriology of the alimentary canal. Much remains to be revealed, but the principles thus far unfolded point unmistakably to a definite relationship between diet and the character of microbic activity within the intestinal tract. Included in this relationship is the part played by lactic acid bacteria. A very brief survey of the salient features will indicate the essential details.

At birth the alimentary canal is sterile, but within a very few days the normal nursling flora becomes unified and characteristically of the lactic acid producing type. The prominent bacteria are anaërobic and of the Bacillus bifidus type. These persist in dominating numbers and activity, until the dietary requirements of the child exceed the nutritional powers of the mother. Then the regimen is reënforced by starches and cow's milk, together with other foods which are qualitatively and quantitatively quite unlike the human milk. Usually the carbohydrate-protein ratio of the food is materially altered. The amount of protein food is increased considerably, while the lactose is reduced and replaced in part by starches. The net result is the creation of a relative deficit in diffusible sugar in the intestinal tract, together with a relative excess of protein. In the lower levels of the alimentary canal the protein residuum may be quite considerable, and carbohydrates in diffusible form may be entirely absent there.

The character of the microbic flora changes with the dietary changes. The obligate lactic acid bacteria decrease materially in numbers, or even quite disappear. More versatile microbes take their place. Prominent among these is Bacillus coli, which can thrive nearly as well upon a protein residuum as upon one containing both utilizable sugars and protein.

The chemical products resulting from this change in the bacterial flora are strikingly different from those characteristic of the normal nursling's flora. Bacillus bifidus produces only lactic acid, but Bacillus coli, and its associated variants, is, or may be, a veritable Dr. Jekyll and Mr. Hyde.

If sugars are present at the levels where it is growing luxuriantly, lactic acid is produced in considerable amount. If carbohydrates are absent, the microbe turns to the protein residua for its energy requirements, and forms from them indol, phenolic bodies and other protein putrefactive derivatives, which are believed by many writers to be important factors in the syndrome of auto-intoxication. Metchnikoff [1] also seems to have acquiesced in this view, that indolic and phenolic bodies are the chemical basis for auto-intoxication.

It is necessary to interrupt the discussion at this point to call attention to the well-established fact that the mere absorption of putrefactive products from the alimentary canal does not induce unfavorable symptoms; indeed, practically every adult enjoying a mixed diet must absorb considerable amounts of putrefactive products daily.[2] Metchnikoff also must have recognized this fact. It seems not improbable that his assumption of the harmful effects of anaërobic bacilli developing in the lower alimentary canal is an attempt to differentiate between the normal or usual absorption of indol and phenols, produced by the colon bacillus, and abnormal amounts or abnormal products formed by the growth of anaërobes in the lowest levels of the intestinal tract.

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[1] See Chapter IV, The Prolongation of Life.

[2] Folin and Dennis state that from 0.2 to 0.3 gm. of phenol are absorbed daily by the normal adult.

The part played by the liver in auto-intoxication seems to have been overlooked. The functions of the liver are of course many. One of the most important, however, is that of oxidizing and subsequently pairing putrefactive products, as, for example, indol, with glycuronic and sulphuric acids, before they are permitted to enter the general circulation. If the capacity of the oxidizing and combining powers of the liver is exceeded or lowered, some of these unoxidized and unpaired putrefactive products may escape into the general circulation and there bring about their slowly cumulative poisoning.

In brief, the great majority of normal adults enjoying a normal mixed diet absorb the chemical basis for auto-intoxication daily from the lower levels of their alimentary canals in the form of bacterial putrefactive products. These pass in the portal blood to the liver. They are oxidized, paired, and therefore detoxicated, or at least materially reduced in potential poisoning power. In this oxidized state, and paired, they gradually leave the body through the kidneys and little or nothing happens. If, on the contrary, the liver functions are disturbed and its oxidizing and pairing powers reduced, these same putrefactive products escape from the liver unaltered. Selecting indol as illustrative of this group of substances, it may be stated that indolemia and indoluria are suggestive of impaired liver function. On the other hand, indicanemia and indicanuria are indicative of unimpaired liver function. The former are abnormal; the latter normal, or nearly so.

To return to the intestinal flora: The ordinary products of bacterial putrefaction produced in the lower levels of the intestinal tract, or even in the higher levels under conditions of stasis or constipation, are as a rule the results of the growth of normal intestinal microbes. Anaërobic bacteria, so far as available information goes (and it is much in advance of that known when Metchnikoff published *The Prolongation of Life*), do not produce significant amounts of indol, phenols, or other substances of the putrefactive group. Some, such as Bacillus welchii (the so-called "gas bacillus"), vibrion septique, and a few others, do form soluble poisons, but the one anaërobe that has been found at all commonly in intestinal disorders, Bacillus welchii, produces its harmful effects from carbohydrate-rich rather than protein-rich diets. Diarrhea rather than constipation is commonly the result of an overgrowth of this anaërobe. Strangely enough, well-soured milk is the best remedial agent in the treatment of gas bacillus diarrhea, except of course a restriction of the carbohydrate in the diet.

Principles of Therapy.—Notwithstanding the discrepancies between the original conceptions of the causation of auto-intoxication and premature senility and present-day opinions, the fact remains that Metchnikoff added a brilliant idea to contemporary medicine in his suggestion of microbic replacement in the alimentary canal. Like so many other ideas, the pattern has been worked out by Mother Nature and has operated for countless centuries in numberless generations of man. The details are best observed in the normal nursling, or in the properly fed but artificially nourished child of corresponding age. The cause, the causative agent and the effect of lactic acid therapy, all are revealed in their simplicity in Nature's nutritional procedure.

The diet of the nursling contains a large amount of lactose in proportion to the protein and the fat.[3] The dominating intestinal microbes of the normal nursling are acidogenic and of the lactic acid type. The feces contain considerable amounts of lactic acid, indicating quite plainly that the entire intestinal tract, microbically speaking, is fermentative rather than putrefactive in character. The intestinal tract, and therefore the urine of the normal nursling, is quite free from bacterial putrefactive products. Herein are all the essential factors for successful lactic acid implantation and lactic acid therapy.

The corner stone is the diet. Without lactose or some other suitable carbohydrate bacteria cannot produce lactic acid. This focuses attention upon two important causes for failure in bacterial implantation, as it is frequently practiced. First, it is obvious that the mere administration of cultures of lactic bacteria, without providing them with carbohydrate to act upon, is inevitably futile. Again, it is not a matter of indifference what carbohydrates are administered. Lactose has several advantages. Lactose is more slowly hydrolized and absorbed than most sugars and it may be fed in larger amounts without producing an aversion. Also, and this is important, the lactase which cleaves the lactose is found in the mucous membrane of the intestinal tract, chiefly the small intestine. Furthermore, the normal intestinal microbes of the colon group utilize lactose readily and form, therefrom, lactic acid in place of indol and other putrefactive products, which are the results of their action upon protein derivatives in the absence of utilizable carbohydrate. It will be seen, therefore, that a diet rich enough in lactose or some other sugar to permit of a sufficient excess to more than balance the absorption from the alimentary canal, thus leaving at all levels a residuum for microbic utilization, is a prerequisite for success in lactic acid therapy.

There are, unfortunately, a few contra-indications to the use of lactose and other carbohydrates. Some samples of lactose contain considerable numbers of gas bacillus spores. Implantation of the gas bacillus with the resulting development of a true gas bacillus diarrhea may result. Also, feeding sugars to patients who have a marked overgrowth of gas bacillus in their intestinal tracts will usually lead to an intensification of the gas bacillus symptomatology. Fortunately, these contingencies are readily guarded against.

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[3] Breast milk contains about 7 per cent of lactose, 1.6 of protein, and some 3 per cent of fat.

Starches are less suitable on the whole for lactic acid bacillus therapy than lactose or saccharose. The maltose and glucose which result from the hydrolysis of the starch molecule are absorbed rapidly from the alimentary canal, leaving but little utilizable carbohydrate for the lactic acid bacilli whose growth is to be encouraged. It may be mentioned in passing that an occasional diarrhea caused by an overgrowth of members of the Bacillus mucosus capsulatus group may result from a heavy starch diet.

The basis for successful lactic acid implantation in the intestinal tract may be said, therefore, to rest upon the proper administration of lactose or other sugar in the diet. Without a suitable carbohydrate source of energy, lactic acid bacilli, either resident or introduced, cannot flourish.

The second factor requisite for success in lactic acid therapy is the microbe. It is very obvious that there are three cardinal principles involved in selecting a lactic acid microbe for intestinal implantation. First, it must be able to grow in the alimentary canal in competition with resident bacteria; secondly, it must produce considerable amounts of lactic acid; and, thirdly, it must under no conditions form harmful products, either acidic or putrefactive.

The majority of bacteria from all sources form lactic acid in varying amounts when they are grown in media containing utilizable carbohydrate. Diphtheria, glanders, typhoid, cholera, coli, paratyphoid, dysentery, Bulgarian bacilli, Bacillus bifidus and Bacillus acidophilus, streptococci, staphylococci, and many others produce considerable amounts of lactic acid from utilizable sugars. Under proper conditions, each and all of the list mentioned specifically would make very good buttermilk from the chemical standpoint. Indeed, it is possible to convert typhoid, paratyphoid, cholera, dysentery, and colon bacilli growing in the alimentary canal of man into potentially lactic acid-producing microbes. Such bacteria, however, are hardly suited for deliberate intestinal implantation. Bacillus bulgaricus, Metchnikoff's sour-milk bacillus, forms considerable amounts of lactic acid, and it is from this viewpoint well suited for the production of sour milk. Unlike typhoid, dysentery, and other bacteria of the intestinal pathogenic group, however, it fails to grow in the alimentary canal of man. The Bulgarian bacillus grows well in the nomadic milk pail, outside the human body, but it is never found in the intestinal tract of man. The ideal lactic acid microbe suitable for introduction in the body will never be found growing spontaneously in the dairy industry; it must be sought for in the habitat where it grows best. Bacillus bifidus and Bacillus acidophilus, two important lactic acid bacilli of the alimentary canal of young children, in whom lactic acid fermentation is taking place normally, do not occur in milk soured by Bulgarian bacilli or other starters. They do not accommodate themselves readily to conditions outside the alimentary canal, although they can be induced to grow in milk cultures, if more rapidly growing types are excluded.

Bacillus bifidus and Bacillus acidophilus are Nature's intestinal lactic acid bacilli. Of all the great group of lactic acid-forming microbes, these two are the ones found in the nursling and adolescent intestinal flora where desirable lactic fermentation is taking place. It is not difficult to predict that these two bacilli are the best suited for intestinal implantation.

There is a gradual shifting of clinical opinion toward this viewpoint, although the suggestion is of long standing. Many observers have described the appearance or reappearance of Bacillus bifidus and Bacillus acidophilus in the intestinal flora of patients in whom dietary changes favorable to their growth have been instituted. These changes may take place even in suitably fed dysentery and typhoid patients. This indicates that a residuum of normal lactic acid bacilli may persist in the intestinal tracts of mankind for many years after the nursling period is passed. Furthermore, it suggests that reinfection of the alimentary canal with these microbes should be a relatively simple and fairly direct procedure, if proper dietary conditions are observed.

The question might be raised—Which organism should be used, Bacillus bifidus or Bacillus acidophilus? It seems probable that the latter is more readily obtainable. Bacillus bifidus is an anaërobe and, therefore, somewhat more difficult to cultivate outside the body. It is much more sensitive to environmental influences than Bacillus acidophilus and not readily obtained from the feces in pure culture.

Inasmuch as Bacillus bifidus and Bacillus acidophilus both lose their ability to grow in the intestinal environment with greater or lesser readiness after they are parasitized upon artificial media (and, therefore, tend to assume a state not unlike that of Bacillus bulgaricus), the evidence on the whole favors Bacillus acidophilus as the prospective therapeutic lactic acid bacillus.

Several details must be carefully observed, if successful implantation is to be accomplished. First, the microbe must be in pure culture.[4] Several so-called acidophilus cultures are sold in various parts of the United States—and this is equally true of so-called acidophilus milks—which are either wholly inert or materially contaminated.

Secondly, the microbe must not be too far removed from the alimentary canal in point of time. Parasitism outside the alimentary tract in artificial media leads to a loss of intestinal adaptation.

Thirdly, the microbe must be introduced into the alimentary tract in some medium in which it is growing vigorously, and from which it may obtain the requisite energy to form lactic acid. It is futile to swallow a capsule of lactic acid bacilli in culture or administer a tablet of dried lactic acid bacteria and expect a miraculous development in the alimentary canal.

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[4] Contemporary writers are frequently indefinite in their descriptions and identification of Bacillus acidophilus. The organisms of the acidophilus type, first isolated by Moro and Finkelstein, are described in detail by Kendall and Rahe.

Fourthly, the diet must be so adjusted that a *continuous* supply of utilizable carbohydrate is available for the microbe to act upon. The amount varies materially with the individual.

Finally, heavy carbohydrate feeding should not be instituted until there is assurance that an overgrowth of gas bacilli shall not take place. Fortunately, milk soured with acidophili will almost always control the action of gas bacilli in the alimentary canal.

Results to be Hoped For in Lactic Acid Therapy.—Lactic acid therapy from the clinical viewpoint can be reduced to two quite distinct types, namely: the use of soured milk with a properly restricted carbohydrate diet to control the symptoms associated with an abnormal intestinal development of the gas bacillus and related forms, and in certain types of constipation, on the one hand; and the administration of a carbohydrate-rich diet, with the implantation of Bacillus bifidus or Bacillus acidophilus, in intestinal infections of the typhoid-paratyphoid-dysentery toxic type, and in the general but poorly defined group of intestinal autointoxications, on the other hand.

In the former, a suitable restriction of the diet, particularly with reference to carbohydrate, and fairly continuous amounts of soured milk will usually result in a gradual amelioration of the symptoms. The symptoms in such cases are quite varied, but careful inquiry will usually elicit the information that in the last analysis they are quantitatively rather than qualitatively different. Diarrhea may be acute, subacute, or intermittent. The duration of the condition may be days, weeks, or months. Relief following proper dietary control and sour-milk ingestion is to be expected about in proportion to the duration of the condition, weeks or even months sometimes elapsing before the patient realizes that a decided change for the better has taken place. Medical texts do not seem to have recognized this syndrome. In the more acute and obstinate cases, the patient enjoys "a state of rude health," neither very ill nor thoroughly well. Many times neurasthenia is diagnosed; it may be and not infrequently is a symptom. Careful inquiry will frequently reveal an unrecognized intolerance for certain carbohydrates, even including starches of one or another kind.

The treatment includes a restriction of sugars, an increase in protein and, to a limited extent, fats, and the administration of well-soured milk,[5] a glassful at a time every few hours. Continued, relatively small feedings of soured milk are better than a few large amounts during the day.

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[5] Milk soured by Bulgarian bacilli is excellent for this purpose. The preformed lactic acid present in Bulgarian and other sour milks seems to be the essential factor, not the microbes themselves.

This peculiar type of intestinal disturbance requires first of all the control of the conditions which permit of the overgrowth of the gas bacillus. It cannot be stated dogmatically that the more chronic cases are caused primarily by the gas bacillus, but it is a significant fact that the same measures that restrict gas bacillus growth in the laboratory restrict the growth of the microbe in the alimentary canal. When the gas bacillus is under control, the gradual building up of an aciduric flora within the alimentary canal should be attempted. Inasmuch as this presupposes the administration of considerable amounts of carbohydrate (lactose preferably), the necessity of controlling the gas bacillus overgrowth first is fully apparent.

Constipation is frequently relieved by the restriction of the protein in the diet, and the simultaneous administration of soured milk. Bulgarian sour milk is usually successful, but acidophilus or bifidus milk, provided the requisite lactose feedings are feasible, is better. The lactic acid acts as a mild stimulant of peristalsis in such cases, precisely as it stimulates peristalsis in the normal nursling. Generally speaking, endogenously generated lactic acid, formed *in situ* by bacteria in the alimentary canal, is more effective than exogenously generated lactic acid formed in the milk bottle, except in gas bacillus infections. In these, as has already been explained, the gas bacillus, growing rapidly, gains the ascendancy over the more slowly growing aciduric microbes, and thereby tends to crowd out the latter.

Putrefactive disorders and toxicogenic intestinal infections are alike in that the microbes forming putrefactive products or poisons do so by acting upon protein. With the exception of Bacillus alcaligenes, which apparently uses no sugars, all of the microbes of the putrefactive-toxic group—coli, proteus, typhoid, paratyphoid, cholera, dysentery, and others—form their obnoxious products from protein. If utilizable carbohydrate can be brought *continuously* to these bacteria, they alter their metabolism from the Mr. Hyde to the Dr. Jekyll type; that is to say, they form lactic acid from the carbohydrate in place of the putrefactive products, or poisons, from the protein.[6]

The dietary treatment of such cases is somewhat unlike that of the gas bacillus type of case in that utilizable carbohydrate (preferably lactose) should be administered in amounts or frequency such that an undigested and unabsorbed residuum of carbohydrate is continuously available throughout the alimentary canal. Also, Bacillus bifidus or Bacillus acidophilus milk should be fed in amounts sufficient to flood the tract with viable aciduric bacteria.

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[6] See Kendall for details.

Two distinct results are desirable: first, to alter the metabolism of the offending bacteria, coli, typhoid, dysentery, or others, from the proteolytic to the carbohydrophilic phase; and, secondly, to introduce and encourage a virile strain of purely lactic acid microbes. Fortunately, the same dietary procedure, properly carried out, accomplishes both desiderata.

The colon bacilli normally resident, and abnormal invaders as well, become lactic acid bacilli under the carbohydrate regimen, and the aciduric bacteria, more tolerant of lactic acid than the proteolytes, gradually or even rapidly supplant the offenders.

Lactic acid therapy is still in its infancy. Its limitations and applications are yet to be determined. The intestinal incubator is a formidable place for well-being or harm. It does not require much imagination, however, to appreciate these possibilities when it is recalled that the average normal adult, enjoying an average mixed diet, excretes daily about thirty trillions of bacteria in the feces. Much light may confidently be expected from a more intimate study of the methods of the greatest internist of all, Mother Nature, who has miraculously safeguarded the immature alimentary canal of the nursling with a natural regimen, correctly adjusted, to induce spontaneous and effective lactic acid protection.

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TECHNIC

CHAPTER VII

PRINCIPLES AND TECHNIC OF ADMINISTRATION OF MEDICINE

JOSEPH C. ROPER

Oral Technic.—Modern pharmacy has so refined the preparation of medicines designed for oral administration in adults that the physician experiences little difficulty. Most drugs may be obtained singly and in a variety of combinations in tablet form in almost any desired dosage. Individual combinations are readily prepared in pill or capsule form and only a little care is required to avoid mixing ingredients which will not retain their original structure and properties. One soon learns that the contents of a capsule of antipyrin and sodium bromid may liquefy and that chloral hydrate and camphor certainly will.

When the quantities prescribed are too large for capsules one may have recourse to powders or fluids. In liquid preparations palatability may be obtained by a little care. A clean bitter taste is not always objectionable, for the tonic still has psychical as well as physical attributes. The choice of form of administration, therefore, will depend on solubility and taste and will be influenced somewhat by psychic considerations. It is well to remember that the U. S. P. Elixirs contain 25 per cent alcohol while many of the Comp. Elixirs of the N. F., such as glycyrrhiza, cardamom and vanilla, contain about 5 per cent.

Greater difficulty is encountered in oral administration of medicine to children. In older children, of course, the cachet capsule and tablet or pill are available as in adults, but the child under three or even five who will swallow a capsule is the exception. These may not be utilized. Tasteless drugs, such as bismuth, may be given in a suitable vehicle or in food, but the administration of quinin and other drugs of disagreeable taste is much more difficult. Luckily the indications do not present themselves as frequently as formerly. Before submitting the child and the family generally to the annoyance of administering a drug as objectionable as quinin from the child's point of view, the diagnosis should be definite. Euquinin (ethyl carbonate) is less objectionable than the other preparation but is not tasteless. It may be given in tablets. The dose should be double that of the regulation quinin sulphate or bisulphate.

Percutaneous Medication.—Medicaments have been introduced through the skin by inunction, by fumigation or vaporization, by electrolysis and by baths. All these methods, while occasionally useful, are uncertain and have been replaced or should be replaced by more accurate modern procedures.

For inunction the sites chosen are those parts of the body where the skin is thinnest and where there is very little hair: axillæ, sides of chest and flank, sides of abdomen and insides of thighs. Mercury is of course the drug most commonly introduced by inunction. The rubbing in may be done conveniently by the hand covered with a rubber glove. Masseurs expert in the treatment of syphilis sometimes employ a short baton, the rounded end covered smoothly by a heavy, almost impermeable rubber or parchment. The method at best is not accurate and the intramuscular method is to be preferred.

Because of their inconvenience and inaccuracy, fumigation and mercurial baths have been replaced by injections even in infants.

Intradermal Schick Test.—As there is considerable natural individual immunity to diphtheria, immunization may be avoided in many cases by the employment of the Schick test. This consists in injecting intradermally about 2 minims of a dilute solution of a diphtheria toxin. This amount contains about 1/1,000 of the minimum lethal dose for a guinea pig. In some cities the material is furnished by the municipality. It may be obtained from medical supply houses. The toxin is furnished in a capillary tube and is accompanied by a tube of salt solution with which it is mixed just before use. After mixing with the salt solution the toxin degenerates rapidly and is not satisfactory for use after ten hours. The injection is made on the flexor surface of the forearm. The needle should be small and sharp. It is introduced into the skin (must not pass through) with the bevel side up. The bevel should be completely introduced. The test of success is the appearance of a small white wheal which is caused by the injecting of 2 to 3 minims of the solution into the skin. Positive reactions appear in twenty-four to forty-eight hours and are characterized by a local area of redness and swelling about 1 cm. in diameter surrounded by a lighter red area. Pseudoreactions produce about the same appearance as true reactions but are prone to appear earlier and disappear more rapidly. True reactions persist for a number of days and leave an area of pigmentation and slight scaling.

Vaccination.—Vaccination against small-pox consists of inoculation with the virus of cowpox. The immunity conferred by a successful inoculation persists for a number of years, differing in different individuals. It is good practice to revaccinate when exposed or in the presence of an epidemic, especially if the previous vaccination has been three or more years. The site chosen is on the arm near the deltoid insertion or on the outer side of the leg, two or three inches below the knee. With a sharp sterile needle the skin is scraped away from a small area (about 1/16 inch) just down to the true skin. There should be no bleeding. The virus is expelled on this spot and thoroughly rubbed in with the side of the needle. The site of inoculation is covered by a pad of gauze with a hole cut in the center, thus protecting but not touching. The gauze may be fastened with adhesive plaster strips above and below. Cages must not be used.

Subcutaneous Medication.—Cleanliness must be the watchword in this form of medication. To this end the syringes best suited for use are the all-glass Luer type. As they are relatively inexpensive, several may be kept on hand. If washed with alcohol and dried before putting away they will always be ready for use. The tips are ground to fit the regulation slip-on needle. Less suitable are those syringes made with glass or part glass and part metal barrel and leather plunger. For pocket case work the so-called military type, constructed entirely of metal, may be depended on to be ready when wanted, but it has the disadvantage of invisibility of the contents. Needles of No. 23 gage and 5/8 or 3/4 inch in length are suitable for ordinary subcutaneous work. For antitoxin and serum administration, needles of No. 18 gage and 1½ or 2 inches in length may be used.

Bacterial vaccines and sera are largely used subcutaneously for prophylaxis, diagnosis and treatment. Subcutaneous vaccination against typhoid is familiar to all. A simple typhoid vaccine may be used, but more commonly a so-called combined vaccine containing in addition several paratyphoid stains is administered. Three doses are given at from five to ten-day intervals, the first for adults consisting of approximately 500,000,000 and the second and third 1,000,000,000 bacilli. For children from one-half to one-quarter of these doses are given, depending on age. The vaccines may be purchased in individual glass ampules containing one to two doses or in 5 to 10 c.c. vials with rubber stoppers through which, after sterilizing by immersion in alcohol, the needle may be plunged.

Stock and so-called autogenous vaccines are used against the common cold, influenza and pneumonia. The results are uncertain and inconstant. For prophylaxis the most commonly used is the catarrhalis combined, containing pneumococcus, Micrococcus catarrhalis, influenza bacillus, Staphylococcus albus and aureus, Streptococcus and bacillus of Friedländers.

The results of treatment with vaccines are uncertain and many vaccines once advanced as helpful are now rarely used.

Diphtheria Antitoxin.—This is usually administered subcutaneously. The antitoxin is marketed in bottles or syringes. The package containing the latter contains also a needle, the blunt end of which should be thrust through the stopper. The piston is usually separate, and after it has been screwed into the plunger washer the syringe is ready for use. Any other form of syringe may be used, but the all-glass is most satisfactory. The needle is attached to the barrel and this and the plunger are boiled separately. The antitoxin is then poured into the barrel of the syringe, the plunger is introduced, the syringe inverted and air expelled and it is ready for use. The needle should be sharp (those on commercial packages usually are not) and should not be too large. Where there is a history of asthma or any reason to suspect anaphylaxis, 0.5 c.c. should be introduced subcutaneously and five to ten minutes allowed to elapse. If there are no anaphylactic phenomena the entire dose may be given. The dose in cases of ordinary severity should be 5,000 units. It is not, as a rule, necessary to repeat the dose but, if indicated, this may be done after twelve hours. In urgent cases the serum should be given intravenously (5,000 units) if possible, as well as subcutaneously (5,000). For immunization the usual dose is 1,000 units for children and 2,000 units for adults. The passive immunity which the antitoxin confers lasts three to four weeks.

Subcutaneous Toxin Antitoxin.—Cases giving a positive reaction to the Schick test may be protected by the administration of toxin-antitoxin mixtures. These may be obtained from supply houses or municipal laboratories. The usual dose consists of four hundred times the fatal dose of toxin for a half-grown guinea pig mixed with just enough antitoxin to neutralize it. As marketed this amount is usually contained in 1 c.c. Three doses are given at weekly intervals. Development of immunity is slow, it being usually three weeks from the time of first injection before a satisfactory amount of antitoxin has been produced. It will be readily seen that if immediate protection is needed antitoxin must be used.

Hypodermoclysis.—Because of its ease of administration fluid is often given subcutaneously in cases where there is no urgent need for haste. Considerable quantities of fluid may be introduced in this way. The apparatus required consists of an irrigating jar and rubber tube and a fair-sized aspirating needle. From twenty to thirty minutes are required to introduce about 500 c.c. The loose tissue under the breast is the usual site of hypodermoclysis, but the loose tissue of the flank or inner side of thigh or axilla may be utilized. The fluid should be at least 105° F. when introduced; 0.9 per cent salt solution is commonly used and naturally edema is a contra-indication. In young children the intra-abdominal and intravenous routes are much to be preferred.

Intramuscular Medication.—Intramuscular medication results in more rapid absorption than subcutaneous but is of course slower in its effects than intravenous. If the substance for injection is not irritating, this method may be employed where intravenous medication is impractical. Diphtheria and tetanus antitoxin may be given very advantageously by this route and it is the mode of choice for the administration of the insoluble mercury preparations. In the treatment of congenital syphilis, neutral neo-arsphenamin is also administered intramuscularly. Quicker action of sedatives and stimulants may be obtained in ordinary hypodermic medication when given intramuscularly. For the latter preparations the site chosen is usually the deltoid or muscular part of the thigh. For diphtheria and tetanus antitoxin, the muscles of the outside of the buttocks, thigh or back may be utilized.

Mercury salicylate in liquid albolene is given into the muscles of the buttocks, choosing the area on each side of the middle line out to the margins of the trochanteric fossæ. A convenient strength for common use is 1 gr. of mercury salicylate to 15 minims. It will remain fit for use for an indefinite period. A one and one-half or two-inch needle of medium bore of slip-on type and a 30-minim syringe should be used and it is well to keep the needles and syringe for this work only. The suspension should be warm, the needle and syringe boiled and the skin sterilized by iodin or cleaned with alcohol. The desired amount of the warm, well-shaken mercury salicylate suspension is drawn into the syringe and the needle plunged straight into the muscles of the buttocks. The syringe is then detached to assure oneself that no vessel has been entered. If no blood appears the syringe is again attached to the needle and the injection made slowly. A cotton ball or pad of gauze is held over the site of puncture for a short time. The injections are usually given at five or seven-day intervals and a course consists of ten injections.

Infants.—The same site, the buttocks, is chosen in infants by Fordyce for the injection of mercuric chlorid and neo-arsphenamin in the treatment of congenital syphilis. The bichlorid is given in palmitin in doses as follows:

1/10 gr. for children of from 2 weeks to 6 months.
1/8 " " " " " 6 months to 1 year.
1/7 " " " " " 1 year to 2 years.
1/5 " " " " " 2 years to 3 years.
1/4 " " " " over 3 years.

The course consists of twelve injections at weekly intervals.

Neo-arsphenamin is obtained in 0.1-gm. to 0.25-gm. ampules. Only neutral neo-arsphenamin should be used for intramuscular work and the ampules should be large enough to hold 5 c.c. After immersion in alcohol the end is broken off and from 2.5 to 3 c.c. of freshly distilled water introduced by means of a syringe. Solution may be hastened by drawing the mixture into the syringe and expelling.

The dosage recommended is:

0.1 gm. for children of from 2 to 12 weeks.
0.15 “ “ “ “ “ 3 months to 12 months.
0.2 “ “ “ “ “ 1 year to 3 years.
0.25 “ “ “ “ over 3 years.

A course consists of six to eight injections at weekly intervals. Two full courses of each should be given with an interval of four to six weeks between, regardless of a negative reaction.

Intravenous Medication.—One of the chief concerns in the technic of intravenous medication is the needle. This should have a sharp point with not too long a bevel. Especially in the administration of an irritant such as arsphenamin it is desirable that one enter the vein easily and quickly to avoid preliminary disturbance of the patient. When the vein is large and prominent it will roll away from a needle with a dull or turned point and, where one must locate the desired vein by touch as in arms well padded with fat, a sharp needle greatly facilitates a successful entry. In intravenous medication in adults the veins at the elbow should be utilized. When prominent, a large vein is easily entered, and when concealed it may be located by palpation and entered with a little more trouble. A small amount of blood drawn into the medication in the barrel of the syringe indicates success, and the injection is made at once. Occasionally when trouble is experienced at the elbow, a vein on the back of the hand may be used. These look easier than the elbow veins but they are more difficult, being smaller and not as fixed, and a fine sharp needle is necessary to success. The indiscriminate employment of intravenous medication has been freely advocated, but caution should be exercised, and it should be employed only where clearly indicated. The blood is surprisingly tolerant of foreign substances which do not cause lysis or agglutination. Sodium salicylate, for example, has been successfully employed intravenously in the treatment of obstinate cases of rheumatic fever at the New York Hospital for several years. Thirty to 60 gr. in 20 c.c. of water are given two to four times a day. The only precaution to be observed is that the salicylate be pure. There may be some local reaction, but there have been no constitutional disturbances.

Circulatory emergencies present the clearest indication for intravenous medication. Digipuratum, 1 c.c., digifolin, 1 c.c., caffein sodium salicylate or benzoate, 5 gr., and adrenalin chlorid, 5 to 15 minims, are the medicaments usually relied on in such emergencies.

The administration of arsphenamin is most satisfactorily carried out intravenously. The arsphenamin must be pure and the water should be freshly distilled. A 15 per cent solution of sodium hydroxid is used for neutralization. The apparatus required consists of a 2½-inch needle of about No. 18 gage, a glass irrigating jar, and sufficient rubber tubing with a short glass tube near the needle. The arsphenamin is dissolved in 30 to 40 c.c. of warm distilled water. It is then neutralized by adding the sodium hydroxid solution drop by drop. A precipitate first forms which dissolves as the solution becomes alkaline. An extra drop or two does no harm. The solution is diluted with sufficient warm sterile distilled water or 0.7 per cent salt solution to make the volume equal to 50 c.c. for each 0.1 gm. of arsphenamin used, that is, 0.6 gm. arsphenamin is properly given in 300 c.c. of fluid.

A tourniquet or 3 or 4-inch gauze bandage is placed about the arm above the elbow in such a manner that pulling on the loose end will release it. A small amount of sterile salt solution is placed in the irrigating jar. The tube and needle are freed from air and one of the large veins of the elbow is entered obliquely. As soon as the vein has been entered blood will appear in the glass tube mentioned above. The bandage is loosened and the salt solution allowed to flow in. As soon as this flow has been demonstrated to be properly established the arsphenamin solution is poured into the jar. It is wise to finish the procedure by allowing more salt solution to flow in after the arsphenamin solution has all been given. A very convenient addition to the arsphenamin apparatus is a three-way stopcock, by means of which the first vein entry may be readily seen and through which salt solution and arsphenamin may be run as desired, using two irrigating jars.

Neo-arsphenamin requires no neutralization and may be given in concentrated solution requiring only a 20 c.c. glass syringe. The dose to be given is dissolved in 15 or 20 c.c. of freshly distilled sterile water at room temperature.

In infants up to one and one-half years intravenous medication may be readily given by means of the longitudinal sinus. The needle, 1½ or 2-inch 18 or 20 gage, with a short bevel guarded to within ¼-inch of the point, is introduced into the vein through the posterior angle of the anterior fontanel. The sinus is reached at a depth of about ¼ inch (6.5 mm.). By this simple procedure 60 to 100 c.c. of 0.9 per cent salt solution or 5 per cent glucose solution may be introduced, as also may neo-arsphenamin.

Infusion.—Salt solution infusion is best given to adults at the elbow. Theoretically the solution should have a strength of about 0.9 per cent. One dram of sodium chlorid in a pint of water gives a strength of about 0.7 per cent. In emergencies a heaping teaspoonful in a quart of boiled water may be used. In hospital work sterile salt solution should be on hand in properly stoppered flasks capable of being heated directly or by immersion in boiling water. The fluid may be run from a glass irrigating jar or rubber douche bag into the vein through a large needle passed through the skin directly into the vein, or the vein may be exposed by incision at right angles to its course and a canula tied in. For the latter procedure a tourniquet, scalpel, scissors, aneurysm needle and catgut are necessary. When the vein has been exposed the distal portion should be ligated and a loose ligature passed under the proximal portion. This is used to retain the canula and later to tie off the proximal portion. The temperature of the fluid ordinarily should be about 105° F., but it may be 5° or 10° higher if indicated. It is desirable that the temperature be kept nearly uniform throughout the operation. Fluid should be run in slowly, about 1 pint in five minutes. From 500 to 1,500 c.c. may be introduced, depending on the reaction. If indicated the operation may be repeated as necessary.

In cases urgently requiring resuscitation Crile has advocated intra-arterial infusion of salt solution or plain water combined with 15 to 30 minims of 1:1,000 solution of adrenalin chlorid. A funnel, rubber tubing, needle and instruments for exposing the artery are required. The needle is introduced against what would ordinarily be the blood-stream and, as soon as the flow of fluid has started, the adrenalin solution is injected into the water or salt solution by a hypodermic needle passed through the rubber tubing.

Rectal Medication.—The use of the rectum as a vehicle for substitute feeding in conditions of necessity or where it is desired to spare the stomach is confined now almost entirely to the giving of glucose solution. This may be employed in 10 to 20 per cent solution in 6-ounce amounts every six hours. The rectum should be emptied each morning by a cleansing enema, which may be repeated later in the day if necessary. Glucose is the least irritating and best absorbed food. The foods formerly commonly used were combinations of raw eggs, peptonized milk, beef juice and whisky. One of these feedings is more irritating, more difficult of absorption, and has no greater available food value than a glucose feeding.

The patient lies on his side or back, with hips elevated and feet drawn up, during the proceeding and should lie quietly for an hour or so thereafter. The meal or solution should be run in slowly, and great gentleness should be exercised to avoid irritation of the mucous membrane. Infusions of normal salt solution in volume up to 1 quart are readily retained and absorbed by the rectum when given slowly with the tube about 9 inches in. For quick stimulating effect ½ to 1 pint of black coffee may be used by rectum.

Where desired, instead of the q. 6 h. procedure, a Murphy drip may be employed for the giving of the salt solution, glucose solution or sodium bicarbonate solution. A simple form of Murphy drip may be made by means of a medicine dropper secured in a larger glass tubing, or barrel of a glass syringe, by a cork perforated with a hole for dropper and also with holes for escape of gas. An artery clamp may be used to compress the rubber tubing above the dropper so as to give the desired flow. The rate of dropping should be from sixty to one hundred and twenty a minute, giving a flow of a pint or more an hour. The fluid should be warm and the reservoir elevated but a short distance above the level of the rectum. It is well to interrupt the performance occasionally for an hour or two, particularly if the patient finds it annoying. The tube may be left in position. It is possible to give too much solution. Six or 8 pints in twenty-four hours should meet indications. In bichlorid of mercury poisoning the administration by the Murphy drip method of acetate of potash in 100 per cent solution is indicated.

Small children tolerate all forms of rectal alimentation and medication very badly, but colon irrigations with solution of bicarbonate of soda solution are very useful in pyelitis and acidosis because from the large amounts used considerable absorption takes place. Medicated suppositories and small amounts of medicated fluids given for retention are usually expelled. In the semistuporous state following convulsions, solutions of sodium bromid and chloral hydrate in 2 or 3 ounces of water may be retained.

Where in infants intestinal intussusception is diagnosed and a surgeon is not available, an attempt may be made to reduce the intussusception of the large bowel by air or water introduced by rectum. General anesthesia is necessary. Water injection may be started with the bag at an elevation of 2 to 3 feet, which may be raised to 4 or 5. The capacity of the large bowel of an infant should be kept in mind. It varies from 12 ounces at six months to 20 ounces at one year. These amounts may be moderately exceeded. The disappearance of a previously palpable tumor or passage of fecal matter in water would suggest success.

Under same conditions air may be injected from a Davidson syringe, the distention of the colon being followed carefully on the abdominal surface.

Where a fluoroscope is available the course and effect of a barium enema can be easily observed.

Liquid petroleum or olive oil is often used by rectum for the treatment of constipation. From 4 to 6 ounces are introduced at night to be retained. In the morning a colon irrigation is given. This procedure is repeated daily for about one week or until the bowels move in the morning without the irrigation. The treatment is given at gradually lengthening intervals as the condition improves. Diet regulation aids in the treatment.

Most drugs given by mouth may be administered with benefit by rectum either in solution or in suppositories. Larger doses than the stomach will readily tolerate may be used. For example, it is the practice at the New York Hospital to give cases of acute rheumatic fever 100 gr. of sodium salicylate by rectum in 6 ounces of water at a single dose, repeated daily as needed. This sometimes supplements and sometimes supplants oral medication. No untoward or disturbing effects have occurred.

When the stomach is disturbed, as at the beginning of many acute illnesses and in biliary or renal colic where no one is available skilled in hypodermic medication, a suppository of 1 gr. of codein or the time-honored opium and belladonna suppository may be advantageously used. The hypnotics veronal, veronal-sodium, luminal, etc., may readily be given singly or in combination with codein, etc., in suppository. The sedatives, such as chloral hydrate, sodium bromid, etc., must, however, be given in solution.

Intraspinal Medication.—This is of course always preceded by lumbar puncture. The site of election in lumbar puncture is the space between the fourth and fifth lumbar vertebræ (on a level with the crests of the ilia) or the space above. It may be performed with the patient sitting with shoulders forward or lying on his side with head flexed and knees drawn up. The latter position is the one necessarily employed in most cases for obvious reasons. A special needle with obturator or an aspirating needle may be used. In adults if the spinous processes are widely separated the puncture may be made in the median line, the point of the needle being directed somewhat upward. Or the puncture may be made a little (about ½ inch) to one side of and just below the spinous process and the point of the needle directed slightly upward and inward. The canal should be reached at a depth of about 2½ inches and entry to it may usually be appreciated by the sensation of having passed through the rather dense posterior ligament. If bone is encountered the direction of the needle should be slightly changed. The direct route between the spinous processes is to be preferred. When properly done no blood should appear. In children the direct route is always used and entry made at from 1 to 1½ inches. For diagnostic purposes from 5 to 10 c.c. should be withdrawn. For the relief of pressure the fluid is allowed to run until it drops slowly, the amount removed varying from 15 to 50 c.c. or more. So-called dry taps are rare but occasionally one is able to confirm at autopsy an exudate so thick that it could not be withdrawn. When serum is to be introduced, it is customary to remove a little more spinal fluid than the amount of serum to be injected. Sera for the treatment of meningococcic meningitis, streptococcic meningitis, tetanus and syphilis are run in slowly from a syringe or by gravity from an irrigating glass. In meningococcic meningitis from 20 to 40 c.c. of warmed serum is injected every twelve hours as necessary. In tetanus from 500 to 3,000 units, depending on age of patient, is injected after dilution with salt solution or sterile water.

For intraspinal treatment of central nervous system syphilis arsphenaminized serum has been used. The patient is given a large dose of arsphenamin intravenously. Four hours later 30 to 40 c.c. of blood is withdrawn into a centrifuge tube. After clotting the tube is centrifuged. Three or 4 c.c. of the serum are pipetted off and diluted with equal parts of salt solution. The mixture is heated at 132° F. for one-half hour. Lumbar puncture is done, spinal fluid drawn off, and the diluted arsphenaminized serum injected.

In poliomyelitis and polioencephalitis sera have been used which have been obtained from patients recovered from an attack. Their value has not been definitely established. Simple lumbar puncture is sometimes useful to quiet the patient and relieve pressure.

Intra-aural Medication—*Incision of Ear.*—This operation, so prompt and efficacious in its effects, is readily performed with the aid of modern electrically lighted auriscopes. An excellent view of the drum membrane can be obtained even in children. In the absence of an electric auriscope and in the presence of an emergency, the drum may be incised with the aid of a reflected light through an aural speculum. Redness or bulging in the presence of a continued fever are indications for incision. A paracentesis knife should be used and the incision made either in the posterior inferior or posterior superior portion, depending on the site of greater involvement. The lower incision should be led backward and upward from the bottom of the membrane, the upper one from opposite the short process backward and upward. The canal should be wiped out and thereafter may be washed out with a warm saturated solution of boric acid from two to four times a day as required by the discharge.

For chronic otorrhea instillation or applications may be indicated, particularly in the presence of granulation tissue. For this purpose a solution of 5 per cent silver nitrate in 5 per cent alcohol or a colloidal silver preparation may be used. Applications require excellent illumination and accurate placing. Applicators may be obtained with chromic acid and silver nitrate on the end ready for use.

Obstruction of Eustachian Tubes.—In obstruction of the eustachian tubes the method most usually employed for dilation is that of Politzer. The only instrument required for this method is a Politzer rubber bulb and a short tube with hard rubber nasal tip. For the application of the method the patient is seated opposite the operator. He is given a small amount of water to hold in his mouth. This he is to swallow at the order of the physician. The nasal tip is held firmly in one nostril and the other nostril is closed by finger pressure. As the pharynx rises at the beginning of the act of swallowing, the bag is compressed. An aural stethoscope may be used to determine if inflation of the middle ear has taken place, but the patient can usually tell when the eustachian tube has been opened by the sudden burst of air entering the middle ear. Several attempts may be necessary. If the tube cannot be dilated eustachian catheterism may have to be resorted to. The technic of this should be acquired under competent instruction.

Foreign bodies or impacted cerumen can usually be removed by syringing. Warm boiled water and a large syringe of 20 or 30 c.c. capacity may be used. For foreign bodies moderate force must be used. The removal of wax is facilitated by preliminary instillation of enough peroxid of hydrogen to fill the canal. The patient should lie on his back with head slightly elevated and ear under treatment near edge. He or an attendant holds a pus basin under the ear. The lobe of the ear should be drawn backward and upward to straighten the canal. Warm water is injected at first lightly and then with enough force to dislodge the wax. The ear is dried out with cotton or an applicator.

Intratracheal Medication.—The intratracheal medication which the general practitioner can carry out will be limited to applications which may be applied to or dropped on to the vocal cords or into the trachea or introduced by means of sprays or inhalations. With the tongue held forward between the thumb and fingers of one hand and the patient breathing deeply through mouth (as in getting view of the trachea in indirect laryngoscopy) a 25 per cent or 50 per cent solution of a silver albuminate preparation, such as argyrol or collene, may be dropped into the trachea. A sharp cough testifies to the success of the maneuver.

Astringent solutions may be sprayed into the larynx and trachea in the same manner if one has an air pressure apparatus, or it may be done with an ordinary spray in cases in which the patient can hold his own tongue forward. Soothing preparations in oil may be carried down by deep breathing while an atomizer is throwing a fine spray into mouth and turpentine, menthol and similar preparations may be inhaled from a steam vaporizer, croup kettle or bowl of hot water. The time-honored mask composed of wire gauze bent to a triangle with a small cotton ball at the apex may be used for inhalation. The usual medicament consists of a few drops of a mixture of equal parts of alcohol, spirits of chloroform and creosote or eucalyptol. Insufflation of starch two parts and iodoform one part may be performed with the same technic as for spray, but a special insufflator or powder blower is necessary.

In children all forms of intratracheal medication excepting that conveyed by steam are unsatisfactory. The benefit derived rarely repays for the waste of strength on the part of the physician and patient. The croup kettle with a mixture of compound tincture of benzoin ℥i to water 1 pint is often useful.

Intubation.—This should not be attempted on the living child without previous practice on the cadaver except in cases of great necessity. With good assistance and great natural ability one might do the operation without previous practice, but the field in which one works is small, the patient is constantly resisting and the operation must be performed rapidly. The child is securely pinned in a sheet. It is held on the lap of the attendant with its feet between her knees. She also holds the mouth gag which is inserted on the left side. Another attendant steadies the head slightly forward. With the proper size tube ready the top of the larynx is located and the epiglottis held forward with the index finder of the left hand. The tube is slipped into the trachea alongside this finger which also helps to detach the tube from the introducer and push it into the larynx. All must be done rapidly and it is best to make several attempts, giving the child a chance to recover between each one rather than to persist in one long effort. Relief of dyspnea and cyanosis are immediate when the tube is in place unless it has pushed down a plug of membrane and is obstructed by the same. If the tube has been put into the esophagus this is easily determined by the examining finger and by the ease with which it is withdrawn. If it is in the larynx and there is no immediate relief of but rather an increase in the distressed breathing and cyanosis, it should be drawn out at once by means of the thread and cleaned. If the thread is left on the tube the child's hands must be secured or he will pull out the tube. The child is fed lying on the nurse's lap with the head lower than the body. He drinks uphill. If the thread is removed from the tube extubation must be performed after recovery, that is, in from three to four days to one week or more. The sooner the tube is removed the better.

Preparations for extubation are the same as for intubation. The tube is located by the index finger of the left hand which also guides the jaws of the extubator into the opening. Moderate pressure on the trachea from the outside by the assistant steadies and partly lifts the tube. Several short attempts are better than one long one. It is said to be possible to remove the tube by pressure from below with the head extended and then brought suddenly forward. The writer has had no experience with this method.

Intubation in the Willard Parker Hospital of New York City has been largely replaced by removal of the offending membrane under direct laryngoscopy. Jackson's instrument is used. The child is properly secured upon his back with his head over the end of the table. The laryngoscope is introduced and the membrane removed by suction.

CHAPTER VIII

PRINCIPLES AND TECHNIC OF THERAPEUTIC PARACENTESIS

JOSEPH C. ROPER

Thoracentesis.—Thoracentesis may be employed as a diagnostic or a therapeutic measure. It may be used almost with impunity, but because serious accidents have occurred on the introduction of a needle into the chest the indications should be clear. In a suspected pleurisy with effusion, flatness, diminished vesicular murmur and voice and a relatively mild fever should be present. However, flatness and clear bronchial breathing and voice with a history of ten days' or two weeks' duration may indicate the presence of fluid. Localized signs of long duration with fever and leukocytosis may indicate exploratory puncture in the search for a small pocket of pus.

Thoracentesis with a large needle may be resorted to in suspected tumors of the lung, the particles of tissue obtained being used for direct examination or for fixation, embedding and section. For exploratory diagnostic puncture a needle is used of 14 to 20 gage, depending on the material which one expects to encounter, and a syringe of about 20 c.c. capacity with good suction. The material obtained for tumor diagnosis should be expelled from the needle into 5 or 10 per cent formalin, from which it may be collected on a filter paper funnel for embedding in paraffin.

For aspiration a Dieulafoy apparatus or a Connell bottle gives satisfactory results. All that is needed for the latter is a bottle of about ten quarts' capacity with a fairly wide mouth (about two and one-half or three inches), a rubber stopper to fit same, with one hole through which passes a short glass tube which is connected with a fairly thick-walled rubber tube with the aspirating needle on the other end. A small quantity, about one-half ounce, of alcohol is poured into the bottle and distributed over the sides by agitation. The excess is poured off, a match dropped in and the rubber stopper put in immediately after the burst of flame that follows the lighting of the alcohol. The needle alone need be sterile.

In pleurisy with effusion the needle is pushed through the skin (previously painted with iodin) between the ribs, an inch or two below the lower angle of the scapula, the patient lying on his unaffected side, partly reclining, with the upper arm extended upward and forward across his face. From 500 c.c. to 1,500 c.c. is the amount usually withdrawn. Where possible, especially in spontaneous effusion, guinea pig inoculation should be done. The great majority of spontaneous pleural effusions are tuberculous.

In exploratory puncture for localized empyema puncture may be guided by X-ray or fluoroscopic examination with the suspected area outlined on the chest wall, or, if these are not available, the point chosen should be that at which the signs, dulness, bronchial voice or breath sounds or increased whisper, are most marked.

Sudden death has occurred in exploratory chest puncture. The mechanism of this is not plain and its very rare occurrence should not deter one where the procedure is indicated.

In children where in the course of what has appeared to be a lobar pneumonia the temperature and leukocytosis remain high beyond the normal period, the presence of pus should be suspected and exploratory puncture done. The writer has seen no untoward results from this practice in children.

Artificial Pneumothorax.—In hemoptysis of a grave or persistent character, in localized cavitation with no tendency to improvement, in lung abscess where there seems a possibility of success and in tuberculosis in which one lung seems relatively clear, the production of artificial pneumothorax is often indicated. In reaching conclusions as to the above, a satisfactory X-ray film of the chest is presupposed. A fairly good general condition and good circulation is highly desirable. The opposite conditions should be regarded as contra-indications. The site chosen for introducing the needle in producing pneumothorax when possible is about the anterior axillary line in the fourth or fifth space (usually roughly on a line with the nipple). Nitrogen is employed when possible because it is more slowly absorbed. The apparatus used at the New York Hospital is the Robinson. Two bottles are used. One bottle is filled with sterile water containing 8 c.c. of pyrogallic acid, the latter to absorb oxygen. The nitrogen gas (C.P.) is forced into the bottle thus pushing the fluid back into the second bottle. The skin at the point chosen is of course sterilized and the skin and deeper tissues anesthetized with a 0.5 per cent or 1 per cent novocain. The needle (a rather fine one and one-half or two-inch one) used in producing local anesthesia may be left in place and used for injecting the gas, or a special needle with obturator and side arm may be used. When the needle is being introduced into the pleural cavity it is attached to the gas tube and the cocks connecting the needle with the manometer are open and the cock to the gas bottle is closed. Oscillations of the manometer will indicate when the pleural cavity has been reached and a negative pressure of 5 to 10 cm. indicates that the needle is in the pleural cavity. The manometer cock is then closed and the gas cock opened and a little gas injected tentatively and readings made as to the negative pressure. This may vary from 3 to 10 cm. If there is no negative pressure another site is chosen. When the pleura is definitely entered gas is run in up to 200 to 300 c.c. or until pain is experienced. The gas inflow is regulated by raising or lowering the bottle containing fluid. A final manometer reading is made and recorded and the needle is withdrawn. The final pleural pressure reading should be negative or slightly (up to 3) positive. Pressure is made over site of puncture for a few minutes. It may be sealed with adhesive plaster. There may be a very little subcutaneous emphysema. If there are no contra-indications 300 or 400 c.c. are injected every other day for a week or ten days or until a satisfactory collapse has been obtained, as demonstrated by X-ray or physical signs. This should be maintained by weekly or bimonthly injections. The patient lies comfortably on the sound side with the arm above the head during the operation. Codein in doses of 1/4 to 1/2 gr. is given to limit coughing and the patient remains in bed for twenty-four hours.

Complications.—As in any thoracentesis the patient may experience so-called pleural shock, characterized by pallor, rapid pulse and dyspnea. It is extremely rare that this is of any gravity. Severe pain is an indication of separation of adhesions and a signal for stopping the injection. If no gas is injected until a negative pressure has been recorded there will be no danger of gas emboli. Effusions sometimes complicate the procedure and may be very persistent; if they do not go on to empyema, no harm results, but the end result may be a very much thickened pleura.

Paracentesis of the Tunica Vaginalis.—A trocar and canula or an aspirating needle and syringe may be used. The position of the testicle should be determined by transillumination and palpation. It is usually posterior. After sterilizing with tincture of iodin and anesthetizing with 0.5 per cent novocain the hydrocele is made tense by the left hand and the needle is inserted with the other hand and the contents are aspirated or allowed to escape. For the cure of the condition from 0.5 to 1 c.c. of 95 per cent phenol may be injected through the same needle. This is spread over the surface by manipulation and the patient is kept abed until the immediate reaction subsides.

Paracentesis Abdominis.—Paracentesis of the abdomen is usually performed with a trocar and canula. It is good practice after sterilizing and anesthetizing the skin to make a small incision before inserting the canula. The point selected for puncture is usually in the midline about midway between the umbilicus and the symphisis pubis. The bladder should be emptied just before the operation. Puncture may also be made laterally far enough to avoid the deep epigastric which lies a short distance from the midline. If the fluid is withdrawn slowly a large amount may be evacuated with no untoward symptoms. If desired a many-tailed bandage may be used to compress the abdomen and compensate for loss of pressure. The operation may be repeated as necessary, a new site for puncture being chosen each time. From one to several quarts may be evacuated.

The position of the patient is usually semireclining. A stitch may be taken in the small incision or it may be dressed with gauze and a firm strip of adhesive plaster.

For introduction of fluid in infants the abdominal cavity is sometimes employed. The needle is gently pushed through the wall and the fluid, usually a salt solution or 5 per cent glucose solution, allowed to run in slowly.

Paracentesis Pericardii.—Paracentesis of the pericardium is performed for diagnostic or therapeutic reasons. In the presence of signs of fluid in the chest and in the absence of pericardial friction rubs, the determining of whether fluid is in the pericardium or pleura may be difficult. Where obtainable X-ray films are of great assistance, readily differentiating the conditions. Where the signs are confined to the left side or to the left side of the chest and lower left chest posteriorly a few cubic centimeters of salt solution colored with methyl blue may be introduced into the pericardium to the right of the sternum and a few hours later aspiration may be done at the area of dulness posteriorly. The presence of the stain would indicate that the punctures entered the same cavity. Careful auscultation over the sternum will often reveal a to and fro friction rub even in the presence of large amounts of fluid. This or a good history of a preëxisting rub in the presence of a suggestive area of dulness indicates aspiration of the pericardium if the condition of the patient suggests such a need—that is, rapid heart, orthopnea, anxiety, etc. The occasional persistence of the friction rub in the presence of a large effusion is due to the fact that the heart anatomically cannot be very far away from the anterior portion of the chest, no matter what the amount of fluid. Fluid at first accumulates laterally and, as it increases in amount, depresses the pericardium posteriorly on either side of the spine, compressing the lungs and pushing them aside, especially the left lung. The accumulation is usually greater on the left side than the right and frequently gives an area of flatness and bronchial breathing at the base of the chest posteriorly close to the spine. If this possibility is not kept in mind, this area may be mistaken for consolidated lung. This posterior dull area is the elective site for aspiration in these large effusions. In smaller effusions aspiration is best done at the outer margin of dulness. The other points often recommended close to the sternum may be employed.[1] An aspirating syringe of 20 c.c. capacity should be used and the aspirator attached later, or more conveniently a three-way stopcock will permit the introduction of aspirating bottle suction when desired. The amount withdrawn depends on the size of the exudate and varies between 50 and 500 c.c.

In aspirating in the fifth or sixth space as advised above the pericardial sac will be reached at a depth of about one inch. The exudate is at times hemorrhagic and may be alarming when first seen because of this. The removal of a small amount is often followed by absorption of the balance and, of course, many small exudates clear up without aspiration. The presence of pus is an indication for resection and drainage.

Paracentesis of Joints.—This is indicated for the relief of persistent, long-continued effusions or for the obtaining of material for examination or culture.

The large joints are the ones usually explored in this manner—the shoulder, elbow, wrist, hip and knee. Asepsis and antisepsis must be very thorough. The skin should be cleaned with soap and water, washed with alcohol and painted with tincture of iodin. Needle and syringe must be sterile and the hands of operator thoroughly cleaned. The tip of the guiding finger should be painted with iodin.

The shoulder is entered posterolaterally between the head of the humerus and the acromial process; the elbow either posteriorly between the olecranon and the head of the ulna or, with forearm flexed, on the outside between the head of the radius and the ulna; the wrist on a line joining the styloid processes on the posterior surface at a point near the radius; the hip from the side just above the great trochanter; the knee from either side of or above the patella, depending on the location of swelling; the ankle from in front about one-half inch above the malleoleus on the inside and three-fourths inch above malleolus on the outside at a point about halfway from the center to the malleolus.

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[1] The angle formed by the base of the xiphoid cartilage and the costal cartilage to the left of the median line is a satisfactory point to tap.—Editor.

CHAPTER IX

PRINCIPLES AND TECHNIC OF TRANSFUSION

Reuben Ottenberg

Blood transfusion is being used with increasing success and frequency. This is due to:

1. A better knowledge of the indications.
2. The elimination of accidents and complications.
3. Improvements and simplifications of technic.

These are the natural headings into which the present chapter falls.

INDICATIONS FOR BLOOD TRANSFUSION

A knowledge of the indications and contra-indications for blood transfusion is important. There is no doubt that many lives are lost because transfusion is not carried out in cases where it is needed, due usually to unfamiliarity of the physician with the subject. A transfusion done at the wrong time may do more harm than good. Therefore, not only the nature of the disease, but the condition of the patient is vital in the decision whether to transfuse or not. I will discuss the subject under the following headings:

1. Hemorrhage and Shock.
2. Hemorrhagic Diseases.
3. Debilitated Conditions.
4. Blood Diseases.
5. Toxemias and Infections.
6. Contra-indications to Transfusion.

Hemorrhage and Shock

Hemorrhage and shock are so closely related in actual practice that it is impossible to discuss them separately. It is safe to say that transfusion is the best of all remedies for severe hemorrhage.

In *acute hemorrhage* the objects of transfusion are: (1) to save the life of a patient by replacing lost blood; and (2) to facilitate the subsequent recovery of the patient. Here transfusion is usually needed as a life-saving measure. The thing to be decided in any particular hemorrhage case is whether the amount of blood lost is sufficient to threaten the life of the patient. While there are various estimates as to the amount of blood whose loss threatens life, these are of little practical value since in practice it is almost never possible to get a correct estimate of the amount lost. For this reason, the appearance and general condition of the patient are our best guides. No hard and fast rules can be given.

The severity of symptoms from hemorrhage depend to some extent on the rapidity of the hemorrhage. The actual symptoms are too well recognized to require description here. Neither the patient's pulse rate, his blood-pressure, nor the blood count is alone a guide. But these factors taken together with the patient's general appearance and state of consciousness may help us to decide. When in doubt in cases of acute hemorrhage, it is a safe rule to transfuse rather than to wait. The prolongation of acute anemia is known to have a deleterious effect on vital nerve centers. And one will seldom do any harm and will almost always do good whether the patient's life is threatened or not.

The question whether it is ever too late to transfuse in acute hemorrhage should be answered with great positiveness. No matter how desperate the condition of a patient is from acute hemorrhage, if the heart is still beating, there is a chance to save him with blood transfusion. There is no more extreme change than one occasionally sees in such almost moribund cases of acute hemorrhage. The entire threat to life is due to one cause, and that can be removed at one stroke by transfusion.

The indications for *transfusion for shock* uncomplicated by hemorrhage are not so different from those for hemorrhage itself. The symptoms, in fact, are very similar; so that at least in cases of internal hemorrhage one is often in doubt as to whether the symptoms are due to hemorrhage or to shock. The unsettled theories as to the mechanism of shock still leave us in doubt as to exactly how transfusion meets the indications. But there is no doubt that two of the outstanding features of shock, the low blood-pressure and the diminished amount of circulating fluid (from whatever cause that may come), are directly met by blood transfusion.

Clinically there is also no doubt of the value of transfusion in shock. Even more than in hemorrhage, the earliest possible time of transfusion is a factor of the utmost importance. A patient who has been in severe shock for a short while can be rescued. One who has been in shock for many hours is often beyond hope. This is one of the reasons why readiness for emergency transfusions is so important. There are cases which one cannot hope to save unless one has beforehand all the knowledge and facilities necessary to put through a prompt transfusion. "In every hospital it should be possible to give a blood transfusion to a patient suffering from urgent hemorrhage within fifteen minutes of his arrival on the premises" (Keynes).

Certain special instances of hemorrhage or shock need to be discussed separately.

Bleeding from Gastro-intestinal Tract.—In bleeding from gastric or duodenal ulcer and in intestinal hemorrhages, particularly those of typhoid fever, the bleeding point often cannot be directly attacked. The question arises in the presence of a severe hemorrhage whether one should transfuse or not. It is sometimes said that gastric or duodenal hemorrhages stop of themselves when the blood-pressure gets sufficiently low. This, of course, is not always true. Many patients have certainly lost their lives from bleeding from gastric or duodenal ulcers. Nevertheless, it is a fact that the majority of such hemorrhages presently do stop. Gastric or duodenal bleeding, therefore, of itself does not necessarily constitute an indication for immediate transfusion. If the patient's condition, however, becomes so low as to threaten life, transfusion certainly should be done even if the patient is still bleeding. Likewise, if the patient has apparently stopped bleeding, but his condition is extremely poor and does not, after a reasonable length of time, show evidence of spontaneous improvement, transfusion should be done.

The fear often expressed that transfusion, by raising the blood-pressure, may again initiate bleeding, has not been warranted by actual experience. On the contrary, it has very frequently happened that a patient, who was still bleeding, stopped bleeding after transfusion. Exactly why this should happen is not clear. It occurs chiefly in instances of very prolonged or repeated hemorrhage from the stomach or duodenum.

What is said above about bleeding from gastric or duodenal ulcer applies to a considerable extent to hemorrhage from typhoid ulcers. Here one is fighting a desperate fight; transfusion is undoubtedly one of the valuable weapons in the armamentarium. One should not hesitate to give repeated transfusions, if necessary, although, of course, in an overwhelming hemorrhage from an intestinal ulcer, transfusion may be useless. In the more common repeated hemorrhages of moderate amount which so greatly sap the vitality of the patient, transfusion undoubtedly saves lives.

In the pretransfusion days the trend of opinion was that cases of severe hemorrhage from the gastro-intestinal tract should not be operated on because the patient's already weakened condition might result in death from the operation itself. To-day with the judicious use of transfusion it is possible to operate on and save cases which would otherwise be beyond help.

Ruptured Ectopic Pregnancy and Postpartum Hemorrhage.—These cases constitute the most acute emergencies. The important point is the value to the practitioner of obstetrics of being in touch with the nearest hospital or other agency where transfusion can be arranged for with the greatest possible speed. There is no other common condition in which prompt transfusion can more certainly save lives.

Transfusions in Connection with Surgical Operations.—What has been said above about shock and hemorrhage applies particularly to many emergencies in connection with surgical operations. Transfusion is being increasingly practiced by conservative surgeons in all debilitated patients preliminary to operation. When possible the transfusion should be performed twenty-four hours before the operation in order that the transfusion reaction, if any occurs, will be over before the operation is begun. Where this is not practical, however, there is no harm in having the transfusion done immediately before, or even during, the operation.

I believe that ether anesthesia inhibits the chill, as I have never seen it occur under anesthesia. After operation, likewise, where the previous condition of the patient has been poor or where operation has involved much hemorrhage, or has been of a type likely to produce subsequent shock, many surgeons prefer to transfuse at once rather than wait for the appearance of collapse symptoms.

In delayed convalescence from surgical operations due to postoperative anemia or prostration, the transfusion of a small amount of blood frequently has a remarkably beneficial effect.

Hemorrhagic Diseases

This group of diseases is one in which transfusion is usually an emergency measure, and it can be counted on to accomplish more than any, if not more than all, other forms of treatment. Nevertheless, in none of this group of diseases is it a specific cure, since in almost all the cases the bleeding is due to one or another variety of blood defect; the new blood introduced only supplies a limited amount of the deficient substance, and when this is used up, as sooner or later it always is, the original tendency to bleed returns. The important diseases in this group are:

Hemophilia.
Hemorrhagic disease of the newborn (melena neonatorum).
Purpura hæmorrhagica.
Hemorrhagic tendency, secondary to various causes, such as jaundice, severe infections, uterine diseases, and blood diseases.

Hemophilia.—In the treatment of cases of hemophilia, whether inherited or acquired, transfusion has a very important rôle. The blood defect is a lack of coagulating ferment, the exact nature of which it is not necessary to discuss here, but the result of which is that the blood clots so slowly as to be of little value in closing bleeding vessels. Therefore, when the patients begin to bleed for any reason whatever, they continue to bleed for hours or days until frequently their lives are threatened.

Clinical experience has shown that in most cases transfusion of a sufficient amount of blood supplies enough of the missing substance to make the patient's blood clot for the time being in approximately normal time. As the result of this, the hemorrhages stop. As these patients usually only bleed at relatively long intervals, occasional transfusions are necessary for many of them; and it is particularly important for their medical advisers to be acquainted with the most rapid and simple way of obtaining a transfusion for them, when such emergencies do arise.

It has been proposed to give these cases small transfusions at regular intervals in the hope of supplying a modicum of the necessary substance as a preventive of hemorrhage. This has turned out to be impractical, because the periods during which patients with hemophilia are free from bleeding are often very long, sometimes lasting for years, and the effect on blood coagulation of a small transfusion is transient.

In hemophilia, of course, the transfusion not only helps to check the bleeding, but brings the patient into better general condition by replacing part of the lost blood.

Melena Neonatorum.—The hemorrhages of the newborn form a group by themselves, clinically rather than etiologically. They are due to a great variety of causes, such as hemophilia, septic infections, jaundice, syphilis.

No matter what the cause, transfusion is almost a specific remedy, replacing lost blood and providing normal blood in its place. Naturally, in those cases in which the hemorrhage is due to some grave primary condition, such as syphilis or general bacterial infection, the patient will only recover if the original condition can be recovered from. In many of the apparently idiopathic cases, however, a single transfusion is completely curative. The results of transfusion in infants seem to be better than in similar cases in adults. Possibly this is because, in proportion to the size of the patient, the amount of blood given is usually much more generous. The technic of transfusion in these cases will be specially discussed below.

Purpura Hæmorrhagica.—What is said above about hemophilia is true to a considerable extent of purpura hæmorrhagica. However, in this disease the blood coagulates normally and the cause of bleeding is essentially a deficiency of the blood-platelets necessary to thrombus formation in the bleeding vessels. In very acute cases of purpura hæmorrhagica, the effect of transfusion is more transient than it is in hemophilia, probably because the transfused platelets disappear from the circulation in one to three days. Nevertheless, in the emergencies which occur in chronic purpura hæmorrhagica and which often continue to recur in the same patient for years, transfusion is very frequently life-saving.

Since the recent introduction of splenectomy (Kosnelson) as a curative measure in these cases, transfusion has a new value in that it enables us to resuscitate the patient and to keep him alive until a splenectomy can be performed.

Secondary Purpura.—The mechanism of the hemorrhagic tendency secondary to various other diseases is not uniform. In practice, however, this makes little difference, as in all cases the blood is more or less affected, and its partial replacement by normal blood is of aid in checking the bleeding.

In *jaundice* this is of particular importance because many of the cases of severe and protracted jaundice (which are those most liable to bleeding) have to undergo surgical operations. In these cases, transfusion should not be allowed to wait until hemorrhage begins, but should be used as a preventive before or during the operation. Its value for this purpose has been amply proved by clinical experience. In cases of very protracted jaundice, if the patient's general condition is poor, it is wise to do a large transfusion (between 1,000 c.c. and 2,000 c.c.) immediately after a bloodletting of a somewhat smaller amount from the patient. In this way a considerable part of the patient's undoubtedly defective blood is replaced by normal blood.

Debilitated Conditions

As a symptomatic measure in debilitated conditions and in anemias, no matter from what cause, transfusion is frequently of use. When employed in this way it takes the place of, and is vastly superior to, all forms of so-called tonic medication. It accomplishes in an hour what otherwise may take months, or may be impossible to accomplish at all. This fact is not sufficiently recognized by the medical profession. Usually a course of several transfusions at appropriate intervals of from one to three weeks has to be planned, because the amount of improvement in hemoglobin and red blood-cells that can be anticipated from any given transfusion is limited (and will be discussed below in discussing the amount of blood to be transfused).

Blood Diseases

When transfusion was first reintroduced by Crile, it seemed reasonable to hope that it would offer help in some specific way in the diseases classed more especially as blood diseases, namely, pernicious anemia, aplastic anemia, and the various forms of leukemia. Experience has shown, however, that this is not the case. Nevertheless, in this group of diseases, transfusion has value, even though it is never in any sense curative.

Pernicious Anemia.—In pernicious anemia transfusion is undoubtedly one of the most helpful forms of treatment. It is of value because a sufficiently large transfusion directly relieves the anemia and improves the general condition of the patient and because, occasionally (but with no regularity and no very great frequency), a blood transfusion induces a remission of the disease.[1]

Remissions occur naturally in the course of the disease, and it has been doubted whether blood transfusion really had any effect in inducing those remissions which occur after transfusion. But any one who has followed many cases of this disease becomes convinced that remissions occur with greater frequency in cases that receive transfusion than in those which do not.

It is not at all certain whether transfusion does prolong life in pernicious anemia. Probably it does, because it postpones the visceral degeneration due to the anemia itself (and undoubtedly one of the factors in the ultimate lethal outcome). But whether transfusion prolongs life or not, it is of value because it makes the patient more comfortable while he is alive. One of the most interesting things about the results of transfusion in pernicious anemia is the disappearance of symptoms secondary to the anemia, such as fever, loss of appetite, and edema, promptly after a sufficient transfusion.

In pernicious anemia repeated transfusions are necessary. It is important not to wait until the patient is in desperate condition before doing a transfusion. In general, any patient whose hemoglobin has become as low as 35 per cent can be bettered, if only temporarily, by transfusion. It is impossible to tell beforehand how long the improvement will last. Transfused blood-cells exist normally for about a month in the circulation of the recipient. Whether they disappear more rapidly in pernicious anemia or not is not certain, but, if they do, the materials in them are probably used over again by the body for the production of new cells.

Aplastic Anemia.—Genuine aplastic anemia is a much more acute and rapidly fatal disease than is pernicious anemia, and is probably of entirely different pathogenesis. The course is so acute that transfusion is usually only of the merest transient benefit.

Leukemia.—In all forms of *chronic leukemia* transfusion is justified occasionally, as a general supportive measure to relieve the anemia which sooner or later burdens the patient. Transfusion has no effect on the course of the disease per se.

In all forms of *acute leukemia* the same thing can be said that was said of aplastic anemia, namely, that the progressive and invariably fatal course is so rapid that practically nothing can be accomplished by transfusion beyond the most temporary buoying up of the patient.

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[1] In some patients the blood picture after transfusion indicates that the blood-forming organs are stimulated to increased activity.—Editor.

Toxemias and Infections

Toxemias and Constitutional Diseases.—There are a few toxic conditions in which transfusion is an exceedingly important therapeutic measure. Of these the most frequently encountered is *poisoning with illuminating gas.* In carbon monoxid poisoning, the trouble is essentially due to the conversion of oxyhemoglobin into carbon-monoxid-hemoglobin incapable of carrying oxygen for respiratory purposes. Transfusion offers a specific, and if properly and promptly applied, practically invariable cure, and in this connection has not yet received the attention that it deserves.

There is no doubt that hundreds of lives could be saved every year, if in all centers where illuminating gas is used there were emergency transfusion stations, where donors belonging to Group I (the universal donor group whose blood can be used in emergencies for any individual) were on hand at all times and where all the accessories for transfusion were ready at any moment. All persons poisoned with carbon monoxid could then be brought at once to such stations and in any case serious enough to require it transfusion could be done at once.

A number of authors have recommended that a venesection should be done immediately before transfusion, and this seems reasonable since it permits us to remove some of the poisoned blood-corpuscles and to do a large transfusion which otherwise might overburden an already strained heart. The amount removed by venesection need not be as large as the amount transfused. Perhaps a venesection of 500 c.c. to 700 c.c. should be followed by a transfusion of 1,000 c.c. to 1,500 c.c. of blood for an adult.

In two other forms of poisoning which have come to notice as the result of modern industrial methods, namely, *benzol poisoning* and *nitrobenzol poisoning,* the blood is directly or indirectly injured. Transfusion is, therefore, of great value, and brilliant results have been reported with it. Transfusion would also seem to be indicated for the same reason in poisoning with *potassium chlorate* and with *potassium cyanid* (when not at once fatal). So far as I am aware it has not yet been put to actual practice in these conditions.

Transfusion has also been advocated in a variety of other toxic conditions, such as *diabetic acidosis, diphtheria, toxemias of pregnancy;* but in these conditions the evidence of its beneficial effect is still lacking. In *uremia,* transfusion has practically no value because it is not possible to replace enough of the patient's blood with transfused blood.

On the other hand, in *dropsy, due to nephrosis,* or chronic parenchymatous nephritis, transfusion is logically indicated, since it replaces anemic and hydremic blood with normal blood containing the proper proportions of serum proteins; and in this condition transfusion has actually proved its value in practice. In all long-standing cases of dropsy of renal origin, transfusion is worth trying. It should here, also, be preceded by a venesection, and the amount of blood transfused should be as large as the patient's circulation will stand.

Transfusion has been tried in *pellagra* and the results reported are promising. I have no personal experience with this condition.

It has recently been shown by Robertson that blood transfusion has an almost specific effect in combating the terrible toxemia produced by *extensive burns* of the skin, and it seems probable that transfusion has a large field in the future for this purpose.

Infections.—Transfusion has been used in all sorts of *acute infections,* such as pneumonia, pyogenic infections, bacterial endocarditis, typhoid fever, measles, influenza. The hope that the introduction of normal blood would help the patient combat the disease has for the most part proved illusory.

On the other hand, in *chronic bacterial infections,* such as chronic osteomyelitis, empyema, and other forms of chronic pyogenic infection, in protracted typhoid fever, dysentery and tuberculosis, the results of transfusion are often most satisfactory. In these conditions the patient is practically always anemic. The overcoming of this one single, but very important, factor often reverses the balance between the forces of immunity and the forces of disease, and starts the patient on the road to improvement. This is one of the important but much neglected fields for transfusion. In this group of diseases, transfusion should be used not once, but repeatedly, until the desired object is accomplished.

Donors previously inoculated against the specific agent of the disease, or supposed to be immune because of a previous attack, have been employed in pyogenic infections, bacterial endocarditis, typhoid fever, scarlet fever and other infections, but the evidence of their greater usefulness is still inconclusive. More extensive studies in this field are needed.

CONTRA-INDICATIONS FOR TRANSFUSION

The chief contra-indication to transfusion is cardiac decompensation. Hypertension, arteriosclerosis, pneumonia and, indeed, any condition causing dyspnea, even without cardiac decompensation, is a relative contra-indication. In these conditions, if transfusion is undertaken, it should be done cautiously and in the form of repeated small transfusions, possibly preceded by bloodlettings. High fever is likewise not an absolute, but a relative, contra-indication, due to the fact that persons who already have high fever are liable to more severe posttransfusion reactions than are others. Where the patient's temperature is very high, if the operation can be postponed to a time of day when the temperature is lower, this should be done.

PREVENTION OF ACCIDENTS BY PROPER CHOICE OF DONORS

Although transfusion is over two centuries old, it has only been put on a safe basis within the last twenty years. It was the occurrence of obscure and terrible accidents when the blood of animals was used for transfusion that led to the complete abandonment of the use of animal blood. Presently it became recognized that such accidents, though less frequent, would occur occasionally when the blood of one human being was transfused into another. The understanding of the cause of this is what has really made modern blood transfusion possible.

The explanation of these mysterious accidents really grew out of Ehrlich's work on immune bodies, developed when the blood of one animal is injected into another animal, and out of a somewhat casual observation made by Maragliano, in 1897, that the blood-serum of one human being occasionally has the power of hemolyzing, and thus destroying, the red blood-cells of another human being. To these observations was added the observation, in 1901, by Landsteiner, that the blood-serum of one human being would frequently agglutinate the red blood-cells of another into small tough clumps which, if they occurred in the circulation, could easily occlude capillaries and small arteries.

Landsteiner went much further than Maragliano, and not only discovered the occurrence of this phenomenon, but discovered a remarkable and peculiarly definite law underlying its occurrence. He discovered that all human beings belong, with regard to their agglutination reactions, in one of four perfectly definite groups. Landsteiner himself only observed three of the groups. The fourth (the rare group) was first noted by two of his assistants, Descatello and Sturli, a year later.

The four groups were first systematically named by Jansky, in 1907, and his terminology is now accepted. Moss, in 1910, redescribed the groups, agreeing entirely in his facts with Jansky, but naming Jansky's Group I as Group IV, and vice versa. This must be kept in mind in referring to the literature.

What then are the characteristics of these four iso-agglutination groups? (Iso-agglutination is the term used to describe the phenomenon in order to distinguish it from hetero-agglutination, which is the agglutination of the cells of one species by the serum of another species of animal, and from auto-agglutination, the agglutination of an animal's red cells by its own serum—a rare phenomenon, occurring chiefly in certain diseases, such as hemolytic icterus, leukemia, and pernicious anemia.)

If one were to get samples of blood from a certain number of adults, say twenty, and to prepare red-cell emulsion and serum from each individual and then to make tests of the agglutinating effect of the serum of each of the twenty individuals on the cells of all of them, he would observe that in some mixtures agglutination occurred, in others it did not. If then (see diagram) one were to place together the records of those bloods which behaved in the same way, certain regularities would at once be apparent.

There would, to start with, be certain individuals, whose red cells were never agglutinated by any other human serum. These would probably be eight or nine in number (corresponding to about 40 to 45 per cent of the population in North America and North Europe). These individuals are known as Group I. When the effect of the serum of these individuals is noted, it is seen that the serum of an individual of this group never agglutinates the cells of another individual of the same group, but does agglutinate the cells of all persons not belonging to this group.

After the setting aside of this first group, a second group would be noticed, almost as numerous as the first, comprising perhaps seven or eight individuals out of the twenty (corresponding to an occurrence of about 35 to 40 per cent in the population). The serum of this group does not agglutinate the cells of the first group, nor of any members of the second group, but does agglutinate the cells of all the remaining bloods. The cells of this group are agglutinated by the serum of the first group and by the serum of certain of the remaining bloods.

A third group would then be easily distinguished, and would be found to be an exact converse of the second group, since the serum of the third group would be found to agglutinate the cells of the second group (as well as of the fourth group), while its cells would be agglutinated by the serum of the second group (as well as of the first). The second and third groups, then, mutually agglutinate each other and are exact opposites. The serum of members of the third group, of course, never agglutinates the cells of other members of the same group. This third group would occur in perhaps three or four out of the twenty individuals (corresponding to an occurrence of about 15 to 20 per cent in the population).

The remaining group, the fourth or rare group, occurs in only 5 to 10 per cent of the population. Its serum contains no agglutinin whatever for any other variety of human blood-cells. The cells are susceptible to agglutination by the serum of members of any of the other groups (although, of course, not by serum of members of the fourth group).

The reader will be greatly assisted in holding this description in mind if he grasps the simple explanation of the facts first offered by Landsteiner, himself, and supported by many exact experimental researches since his day.

All of the facts can be explained if one supposes that there are two agglutinable substances (known as agglutinagens A and B) in the red blood-cells, and two agglutinative substances (agglutinins α and β) in the serum.

If red cells contain A alone, they can only be agglutinated by serum that contains α. If they contain B alone, they can be agglutinated only by a serum which contains β. If they contain neither A nor B, then they are inagglutinable by serum containing either or both of these agglutinins. And, if the cells contain both A and B, they can be agglutinated by serum containing either agglutinin.

It will at once be seen by reference to the chart that the serum of Group I must contain both agglutinins α and β, since it agglutinates the cells of all the other groups. Correspondingly, the cells of Group I contain no agglutinogen whatever (otherwise they would be agglutinated by their own serum).

The agglutinable substance of Group II cells (in virtue of which they are agglutinated by the serum of Group I and Group III) is called A and the agglutinin of Group II serum (in virtue of which it agglutinates the cells of Groups III and IV) is called β. The serum could not contain the other agglutinin, α, or it would agglutinate its own red cells.

Group III cells have agglutinable substance B (in virtue of which they are agglutinated by the serum of Groups I and II), and the serum of Group III has agglutinin α (in virtue of which it agglutinates the cells of Groups II and IV).

Group IV cells have both agglutinogens, A and B, and are therefore agglutinated by the serum of all the other groups. Group IV serum has no agglutinin whatever.

In the course of time a number of important additional facts have been discovered about the occurrence of these groups. The group characteristics, when fully developed, are permanent throughout the life of the individual. The strength of the agglutinin as well as of the susceptibility to agglutination may vary greatly from time to time (due to unknown causes). The group characteristics are sometimes but not always fully developed at birth. More frequently it is the agglutinin which is lacking, the cells showing the agglutinability which is characteristic of the individual's future group. By the end of the first year of life almost all, and by the end of the second year, practically all individuals show the group characteristic fully developed. Moreover, the groupings are inherited in a definite and regular way according to Mendel's law.

These recent facts are probably the explanation of the old clinical tradition that it is best to use a close relative, such as brother or sister, as donor for transfusion. Of course, on the theory of probability, those who have a common heredity are more likely to belong to the same blood group than are total strangers. But the probability is not sufficiently great to warrant the omission of blood tests.

Before going on to the practical application of these remarkable facts to blood transfusion, it is necessary to describe the occurrence of isohemolysis (the laking of blood-corpuscles by serum of another individual of the

FIG. 1.—CHART ILLUSTRATING HEMOLYSIS AND AGGLUTINATION AMONG TWENTY PERSONS

		I Serum Agglutinins α and β								II Serum Agglutinin β							III Serum Agglutinin α			IV Serum No Agglutinin	
Hemolysin →		α	α	β	β					β							α				
Hemolysogen ↓		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
I. Corpuscles No Agglutinogen	1																				
	2																				
	3																				
	4																				
	5																				
	6																				
	7																				
	8																				
II. Corpuscles Agglutinogen A	9	+	+	+	+	+	+	+	+								+	+	+		
	10	+	+	+	+	+	+	+	+								+	+	+		
	11	+	+	+	+	+	+	+	+								+	+	+		
	12	+	+	+	+	+	+	+	+								+	+	+		
	A 13	+ H	+ H	+	+	+	+	+	+								+ H	+	+		
	A 14	+ H	+ H	+	+	+	+	+	+								+ H	+	+		
	A 15	+ H	+ H	+	+	+	+	+	+								+ H	+	+		
III. Corpuscles Agglutinogen B	16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
	B 17	+	+	+ H	+ H	+	+	+	+	+ H	+	+	+	+	+	+					
	18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
IV. Corpuscles Agglutinogens A and B	A 19	+ H	+ H	+	+	+	+	+	+	+	+	+	+	+	+	+	+ H	+	+		
	B 20	+	+	+ H	+ H	+	+	+	+	+ H	+	+	+	+	+	+	+	+	+		

H = Hemolysis + = Agglutination

same species). For a number of years this phenomenon was thought to be connected in some way with disease. However, after the agglutination groups had been worked out, it was discovered, independently and simultaneously, in 1911, by Moss and by Graefe and Graham, that the occurrence of isohemolysis follows (except for one important fact) the same law as does the occurrence of iso-agglutination, the two kinds of reactions being separate but exactly parallel.

There are two isohemolysins α and β in the blood-serum and they act on two corresponding susceptible substances A and B (hemolysogens A and B) occurring in the blood-cells. The hemolysins α or β never occur save in the presence of the corresponding agglutinins, α and β, and the susceptibilities to hemolysis (hemolysogen A or B) occur only in the presence of agglutinogen A or B. The exception to the rule and the explanation of the apparently capricious occurrence of isohemolysis is this: that the hemolysin α or β may or may not be present in serum when the agglutinin α or β is present, and the susceptibility to hemolysis (hemolysogen A or B) may or may not be present in cells which contain the corresponding agglutinogen A or B. In general the hemolysins in the serum and the susceptibility to them in the cells occur with much less frequency than do agglutinins and agglutinogens.

Thus, if we were to observe the occurrence of hemolysis in the mixtures of the twenty bloods described above, we would find that hemolysis had occurred in some instances, but that it never occurred in mixtures in which there was no agglutination (see chart).

It is seen from the practical point of view that if one is sure that no agglutination occurs on mixing any two given human bloods, one is then certain that hemolysis will not occur.

In practice, the test for agglutination is much simpler and quicker than that for hemolysis. Agglutination occurs in a few minutes at room temperature. Hemolysis takes a considerably longer time, requires incubation at body temperature, and depends on the freshness of the serum (since the phenomenon of hemolysis involves the action of complement found only in fresh serum). For these reasons, in transfusion work, although hemolysis in the body is by far the greater danger, the agglutination test is, as a rule, the only one done, and is for practical purposes the only one necessary.

Transfusion Tests

When the facts about agglutination and hemolysis first became known, it became the rule to perform, before transfusion, mutual tests of the serum and cells of donor and patient, and to exclude as donors those persons whose blood showed either hemolysis or agglutination when mixed with that of the patient.

It was presently shown, by Moss, Brem, Minot, and others, that the same object could be accomplished in a more rapid and simple way by determining, through the use of bloods of known group, the agglutination groups to which the patient and the proposed donors belonged. Then an individual in the same group as the patient is selected as donor, since the sera of individuals belonging in the same group never agglutinate or hemolyze each other's cells.[2]

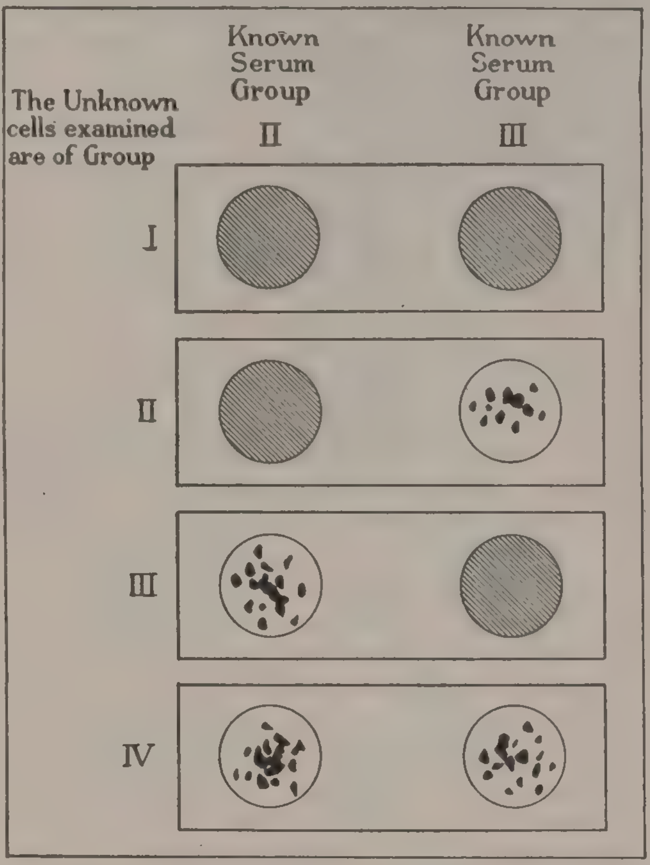

Fig. 2.—Method 1. Determining the Group by Examining the Red Cells.

To determine the group of an unknown blood it is necessary to find out whether it contains A or α and whether it contains B or β. Reflection will show that there are three possible methods:

1. One may detect the presence in the corpuscles of agglutinogens A and B by testing the cells of the unknown blood for agglutination by serum of an individual of known Group II (containing β) and by serum of an individual of known Group III (containing α).

2. One may test for agglutinins α and β in the serum of the unknown blood by testing its agglutinative effect on the cells of an individual of known Group II (containing A) and of known Group III (containing B).

3. One may test both serum and cells of the unknown group against cells and serum of a known Group II individual or a known Group III individual. Thus, if one has on hand serum and cells of an individual known to belong to Group II and wishes to determine the group of an individual of unknown group, one has to make reciprocal tests of serum and cells. If the unknown individual belongs to Group I, his cells will fail to be agglutinated by the Group II serum (indicating the absence of substance B and, therefore, the presence of agglutinin β), while his

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[2] The recent article of Guthrie and Huck has shown that, while there are no exceptions to the rule that members of the same group never agglutinate each other, there are certain subgroups, the existence of which could occasionally, though very rarely, lead to errors in grouping (Johns Hopkins Hospital Bulletin, February, March, April, 1923). On this account, wherever time permits, it is advisable, in addition to determining that the donor is in the same group as the patient, to perform mutual tests, using the serum of each against the cells of the other. Where the case is urgent, however, this can be omitted, as clinical experience of many thousands of blood transfusions has shown that when donor and patient are in the same blood group no serious hemolytic or agglutinative reaction need be feared.

serum will agglutinate the known Group II cells (indicating the presence of the agglutinin α and, therefore, the absence of substance A). If the individual belongs to Group II, no agglutination will occur in either mixture. If the individual belongs to Group III, his cells will be agglutinated by the known Group II serum (indicating the presence of substance B), and his serum will agglutinate the known Group II cells (indicating the presence of agglutinin A). If the individual belongs to Group IV, his cells will be agglutinated by the serum of the known Group II (indicating the presence of substance B), and his serum will fail to agglutinate the cells of the known Group II (indicating the absence of agglutinin α in the serum and, therefore, the presence of substance A in the cells).

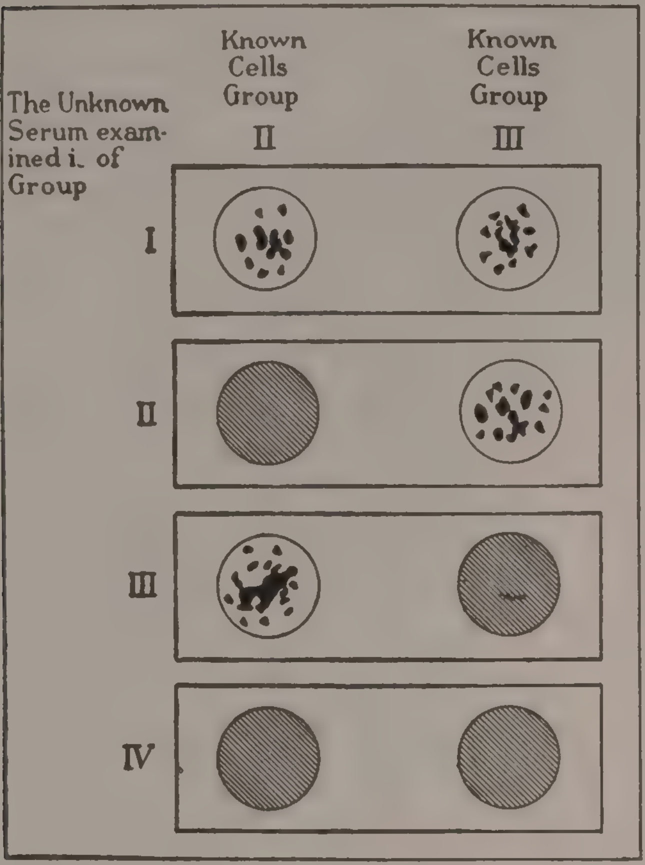


Fig. 3.—Method 2. Determining the Group by Testing the Serum.

If the known blood on hand is of Group III, a similar line of reasoning is followed (see illustration).

Of these three general procedures, the use of known serums, the use of known cells, or the use of cells and serum of a known individual, the first is the simplest and surest, and, therefore, the method of choice for ordinary work. It is important, however, to understand the second and the third methods, because emergencies may arise in places and at times where known Group II and Group III sera are not at hand, and where these other methods may be of value. The second method is frequently used in case of doubt to confirm the results with the first method, or, even when there is no doubt, to make the result absolutely certain.

In view of the recent articles on subgroups it is necessary to use both methods, that is, using the individual's cells against known serum and his serum against known cells, before one can assign his group with complete sureness. And while in ordinary routine work one will only very rarely assign the wrong group if one sticks to either the first or the second method, it is wisest to use both methods.

To obtain serum, either from known Group II and Group III individuals, or from the patient (in case Method 2 or 3 is to be used), it is necessary to perform venipuncture, usually of a vein of the forearm. After the blood has clotted in a test tube, clear serum is obtained by centrifugalization. Smaller amounts of serum may be prepared from a needle puncture of the ear or finger tip, by collecting the drops expressed in a capillary pipet which is then sealed off in a flame and centrifuged. The serum may be kept in sealed tubes on ice for many months, and may be preserved from bacterial contamination by the addition of 0.25 per cent of chloroform or by the addition of 0.25 per cent of phenol.

To prepare red-cell suspensions about five drops of blood, either from a vein or from a needle puncture, are collected in a cubic centimeter of 3 per cent sodium citrate, or of 0.9 per cent sodium chlorid. If hemolysis is to be tested for, as well as agglutination, then the cells have to be washed by repeated centrifugalization and resuspended in fresh saline solution. If only agglutination is to be tested for, as is usually the case, the washing is superfluous, and the cell emulsion is simply diluted with saline solution 0.9 per cent until it is about the density of a 3 per cent cell suspension.

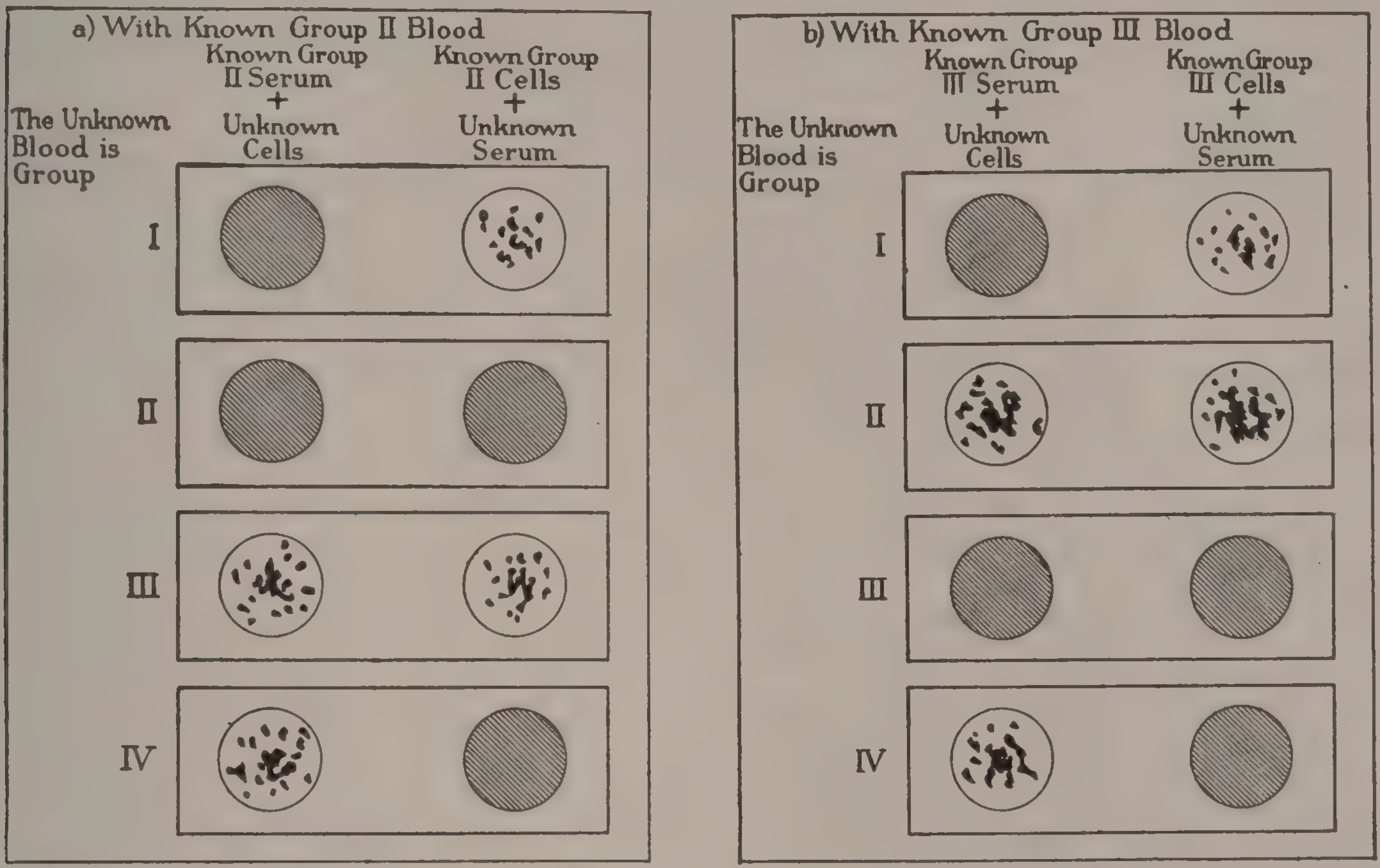

a) With Known Group II Blood
Known Group II Serum + Unknown Cells
Known Group II Cells + Unknown Serum
The Unknown Blood is Group
I
II
III
IV
b) With Known Group III Blood
Known Group III Serum + Unknown Cells
Known Group III Cells + Unknown Serum
The Unknown Blood is Group
I
II
III
IV

Fig. 4.—Method 3. Determining the Group by Mutual Tests with a Known Blood of Group II or Group III.

In laboratories it is easy to measure this, but for practical purposes it is not essential to measure the strength of this emulsion exactly. A simple test for the correct dilution of the emulsion is as follows: A drop of an emulsion of a correct strength, if allowed to fall on a glass microscope slide from a pipet and to spread on the slide so as to have a diameter of approximately one-half inch, should just allow print of the kind used in the articles in the *Journal of the American Medical Association* to be read through it. When in doubt, the emulsion should be made rather too thin than too thick, as error is less likely with a thin than a thick emulsion.

In the actual technic of the agglutination tests, a number of different methods are in use. Any of them will give correct results in the hands of an expert who is acquainted with all the sources of error. I shall only describe in detail the method of Vincent, since I regard it as the method of choice.

The technic is extremely simple. One drop of serum is placed on a slide and into it is allowed to fall one drop of cell emulsion. (This is better than platinum loopfuls, because with the latter the amount is rather too small.) The slide is tilted and rotated gently so that the cells are uniformly distributed; this is repeated every couple of minutes. Agglutination is easily seen with the naked eye in one to ten minutes at room temperature. The microscope is not needed and should not be used. Genuine agglutination is always visible to the naked eye. The observations should never be extended longer than fifteen minutes. The method has the added advantage that the dried tests can be kept as permanent records.

When the tests are made with serum of known Group II and Group III to determine the group of an unknown individual whose cells are tested, the reading of the group from the two mixtures is an exceedingly simple matter (see Fig. 2).

1. If the cells are agglutinated by neither serum, the individual belongs to Group I.
2. If agglutination only occurs in the serum of Group III, the individual belongs to Group II.
3. If there is only agglutination in the serum of Group II, the individual belongs to Group III.
4. If both Groups II and III sera produce agglutination, the individual belongs to Group IV.

Precautions for Avoidance of Error in Tests

The agglutinative power of sera gradually diminishes, no matter how they are kept. Different specimens vary, some deteriorating very rapidly, others hardly at all. Sealed samples kept on the ice retain their strength for long periods. None of the known methods of preserving sera is entirely satisfactory. For these reasons every test must be done in duplicate with *two different* sera of each test group (II and III), and test sera must be shown to be active at the time of the tests. This must be controlled by using them against known Groups II and III cells, within at most a few days of the tests.

Agglutinative sera vary greatly in strength. A test serum must not only be shown to be of the correct group, but to be highly potent before it is taken into use.

Hemolysin never occurs in serum without the corresponding agglutinin. Complete hemolysis can hardly be overlooked and may usually be regarded as the equivalent of agglutination in assigning the group. If hemolysis occurs, agglutination can nevertheless be demonstrated, either by first inactivating the serum and washing the red cells, or by keeping the test from the start at ice-box temperature. Because it favors hemolysis, incubation in the warm is disadvantageous. Observations should be made at room temperature.

Non-specific agglutination can occur if the mixture is allowed to become partly dried. This is avoided by ending the observation in ten, or at most fifteen, minutes (which is ample time if the cells are stirred from time to time). As Karsner and Koeckert have shown, the use of dried and then redissolved serum is not reliable.

Settling of cells is one of the commonest sources of mistakes. The cells settle to the bottom in a compact sheet, which if only slightly stirred looks like massive agglutination. The remedy is through mixing before results are read; this will make a smooth emulsion of merely settled cells, while it will accentuate real agglutination.

The use of the microscope is a source of confusion. Rouleaux formation is sometimes hard to distinguish from fine agglutination. In every instance in which the doubt has been raised by microscopic examination and settled by examination of the person's serum as well as cells, the naked eye observation has turned out to be correct, the microscopic confusing.

Too thick a cell emulsion must be carefully avoided. If the emulsion is much too dense, some of the cells may remain unagglutinated and mask the agglutination of the others. This is a common cause of mistakes.

The group characteristics are not always fully developed in young children. Occasionally one or the other characteristics of the group is lacking in older children or adults. These belong to the so-called subgroups which have been recently described by Guthrie and Huck and their occurrence can easily lead to mistakes in grouping. On account of this possibility one should examine the serum as well as the cells in all cases where this can possibly be done. It is particularly important to do this in selecting test sera and test cells to use in grouping. It is also on this account that it is safest to repeat the tests if a second or third transfusion is done, particularly if the patient is a child.

Auto-agglutination is an exceedingly rare phenomenon, but if present can lead to mistakes. It occurs only at a lower temperature than that of the body. It is easily detected and ruled out, if only the possibility of its occurrence is kept in mind. On account of this, the control test of a drop of cell emulsion with saline solution, or if possible with a drop of the patient's own serum, should always be examined.

The serum of persons who show this rare anomaly to a marked degree sometimes has the power of agglutinating the red cells of all other human beings, even of those of Group I. In such a case it is not certain whether transfusion could be safely practiced. The same may be said of autohemolysis which is a still more rare phenomenon.

Choice of Donors

Suppose that one cannot find a donor in the same group as the patient, what is one to do?

Certain theoretical considerations, backed up now by a large amount of practical experience, have shown that in this case it is safe to choose as donor an individual whose red blood-cells are not agglutinated by the patient's blood-serum, even though the donor's serum may agglutinate the patient's blood-cells.

Why is this?

It depends essentially on two facts. The first is that agglutinins are present in limited amount so that agglutination is not active when the serum is diluted beyond a certain point, usually 1 to 30 or 1 to 40. The second is that the intensity of agglutination by a given amount of agglutinin depends on the number of blood-cells to be acted on. When the number of red cells is large for the amount of agglutinin, then each cell is only feebly sensitized, and agglutination is very slight. If the amount of blood-cells present is large enough, the cells may absorb practically all of the agglutinin present, and yet not be sensitized enough to show any agglutination.

Now, in a transfusion, the amount of blood transfused seldom exceeds (even when the patient has had a hemorrhage) one-tenth of the volume of the patient's own blood. This means that, if the transfused blood-plasma contains agglutinin for the patient's blood-cells, this agglutinin is diluted at least ten times by the patient's own blood-plasma. Furthermore, this diluted agglutinin, even when the patient is quite anemic, has to be distributed among a relatively enormous number of red blood-cells (as compared with the dilute emulsions in which, in a laboratory, the titer of agglutinin is usually found to be around 1 to 30 or 1 to 40). The result is that, in this case, the individual cells are only slightly sensitized, and agglutination, if it occurs at all, is so feeble as to cause no serious trouble.

On the other hand, it is seen at once that when the agglutinin is in the patient, and the susceptible cells in the donor, exactly the reverse holds true. The number of blood-cells is relatively small and the amount of agglutinin relatively large, and it is in these instances, as one would expect, that accidents occur.

Added to these safety factors is the fact that agglutination is not so sharp at body temperature as it is at lower temperature (in contra-distinction to hemolysis which is much more pronounced at body temperature than at lower temperatures).

The same considerations detailed above for agglutinins hold also for hemolysins, with these additional facts: that frequently, although not regularly, there is in the plasma of an individual an unknown substance called antihemolysin which protects his cells up to a certain point from hemolysis; and the fact that hemolysins do not occur with nearly so great a frequency as do agglutinins. It is this more than anything else which explains the relative immunity from accidents where no tests can be done.

Since the blood-cells of Group I are not agglutinated by other human sera, Group I blood can always be used in emergencies for a patient belonging to any group. Group I is, therefore, often called the "universal donor" group. This does not mean that the use of a Group I donor for a person of Groups II, III or IV is as good as the use of a person of identical group. I have seen mild symptoms of hemolysis (jaundice) occur after such transfusions. But in emergencies the blood of the "universal group" can be trusted not to cause serious accidents. Although this fact was pointed out as long ago as 1911, it first received general recognition during the late War, when persons belonging to Group I were kept on hand at casualty clearing stations so that their blood could be used in emergencies without further tests.

It is, of course, also obvious that, if Group I is the universal donor group because its red cells are inagglutinable, Group IV must be the universal recipient group, because its serum contains no agglutinin, and, therefore, cannot agglutinate the cells of any donor used.

Furthermore, suppose that not only is there no time or opportunity to get a donor of the same group, but that there is no opportunity to do any tests whatever. What are the chances of trouble and what should one do? Considering the percentile proportion of individuals in different groups, and the fact that Group I is the universal donor and Group IV the universal recipient, a simple arithmetical calculation, first presented by Karsner, shows that the possibility of accidents only exists in about 36 per cent of the cases if one chooses the donor at random.

In addition to this, even when the possibility of accidents is present, the safety factors discussed above offer a considerable amount of protection, so that the chances of a fatal result from a donor chosen at random are not very great. Experience in the days before tests were made shows that serious accidents can be expected to occur in less than 5 per cent of the cases.

One has, in addition, the control of the transfusion in his hands, provided the transfusion is not given too rapidly. As the first symptoms of hemolysis show themselves within a few minutes, it is possible to stop a transfusion in case these occur before enough blood has been introduced to do serious damage. For this reason, in a situation in which the patient's life would be endangered by waiting for the performance of tests, it is better to go ahead and do a transfusion with any donor at hand, rather than take the greater risk of waiting.

The selection of suitable donors is an important part of blood transfusion. Beside the possibility of blood incompatibility, one has to consider the possibility of the transmission of disease from donor to patient, the general physical condition of the donor, and his ability to give the amount of blood required.

With regard to the transmission of disease, only those diseases known to affect the blood-stream in persons apparently in good health are of importance. The outstanding diseases in this group are syphilis and malaria. Of these, syphilis is by far the most vital. Except in emergencies when a friend or relative of the patient is used as donor, and when the moral responsibility for excluding syphilis can be put (so far as that is possible) on the donor himself, no one should be used as donor for a blood transfusion who has not had a recent physical examination and Wassermann test. Even a negative Wassermann test is no absolute guaranty of the absence of syphilis, since it must be remembered that old or untreated cases of syphilis often have a Wassermann test which varies without known cause between negative and positive.

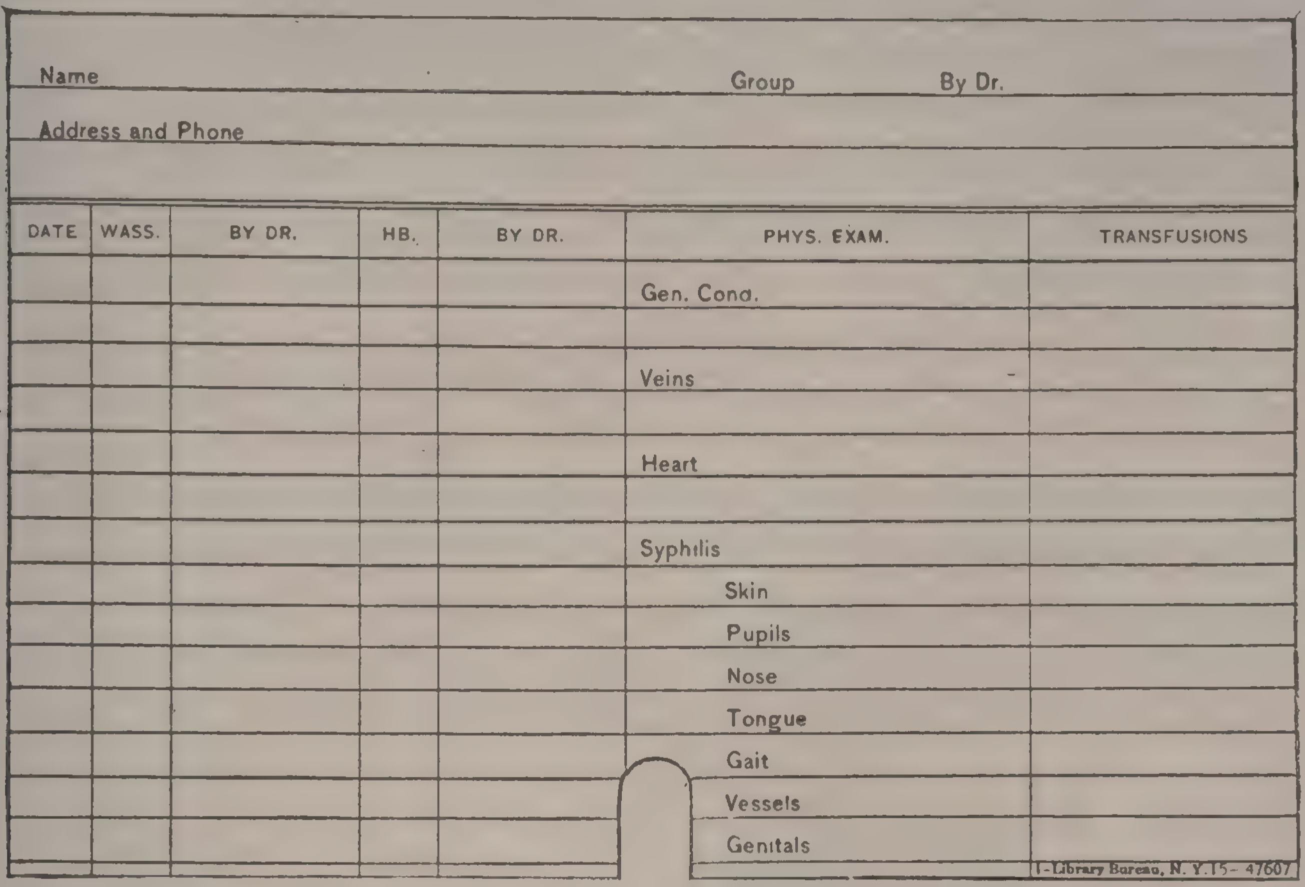
Although the possibility of the transmission of malaria is present, and several cases have been recorded in which it has occurred, chronic malaria is so relatively rare in this country that the search of the blood of an apparently healthy man for plasmodia before he is used as donor is usually dispensed with. But in regions where malaria occurs, this search should always be made.

Aside from this, a hemoglobin estimation should be done on the donor. This is particularly important in the case of the so-called professional donors who give blood at intervals for pay. These men are often misguided enough to offer themselves to different doctors and different institutions so often and at such close intervals that they become extremely anemic.

In institutions where blood transfusions are frequent, it is very convenient to advertise for donors at regular intervals. The men who offer themselves are then examined physically and their blood tests are made. The data thus obtained are catalogued and if the catalogue cards are arranged alphabetically according to the group of the donor under the headings, I, II, III, and IV, it becomes an easy matter, when transfusions are called for, to select and send for one or more donors of the desired group. Such a catalogue card, which I have introduced into use at Mount Sinai Hospital, is shown in the accompanying illustration (page 237).

In view of the steady increase in the use of blood transfusion it is not improbable that in the near future "donor exchanges" will be established in large cities.

In the physical examination of the donor it is important to notice whether the proposed donor has large and accessible superficial arm veins. Those whose veins do not answer this description had best be rejected (excepting in emergencies when they may have to be used and when their veins usually require an incision instead of the usual needle puncture).



Name Group By Dr.

Address and Phone

DATE	WASS.	BY DR.	HB.	BY DR.	PHYS. EXAM.	TRANSFUSIONS
					Gen. Cond.	
					Veins	
					Heart	
					Syphilis	
					Skin	
					Pupils	
					Nose	
					Tongue	
					Gait	
					Vessels	
					Genitals	

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FIG. 5.—CATALOGUE CARD FOR CLASSIFYING PROFESSIONAL DONORS.

TECHNIC OF TRANSFUSION

Since I began to do transfusion in 1907, the technic of transfusion has undergone vast improvement and simplification. At that time the direct artery to vein anastomosis was the only method used (the syringe transfusions of a century before having been forgotten). Subsequently, Lindeman introduced his syringe-canula system. This was modified and improved by Unger's stopcock apparatus, and finally the use of sodium citrate as an anticoagulant was introduced independently by Agote, by Weil, and by Lewisohn, and the use of paraffin-coated vessels for the prevention of coagulation by Kimpton and Brown.

Aside from these methods, each of which depended on a special principle, a large number of modifications have been introduced. To-day there is no universal agreement as to the best method, and there are some things to be said in favor of each of the outstanding methods, and certain situations in which each of them may be advantageous.

I shall describe in detail only the sodium citrate method, and the syringe-stopcock method of Unger. I believe that these two methods together are sufficient to cover present requirements. The paraffin-tube method has no great advantage over the syringe methods. It has the disadvantage that the veins usually require incision, that the preparation of the paraffin containers is troublesome and that the slightest slip in the technic may cause clotting in all of the removed blood before it is injected into the patient. Nevertheless, in the hands of those expert in its use, the paraffin-tube method is said to give excellent results and I do not mean to decry its use.

Sodium Citrate Method

The sodium citrate method in most emergencies and in much routine work is the method of choice. It is the only method so simple that without special training it can be applied by any medical man.

It depends on the fact that an amount of sodium citrate so small as to have practically no toxic effects is sufficient to prevent the coagulation of blood. Lewisohn worked out the minimal proportion of sodium citrate required for this purpose and found it to be approximately 0.2 per cent. In practice, however, one occasionally encounters bloods of unusual coagulating power. It is, therefore, the custom to make the concentration of sodium citrate 0.25 per cent. This concentration is attained in transfusion in the simplest and easiest way by measuring out one portion of 2.5 per cent sodium citrate solution in distilled water and diluting it with nine volumes of blood.

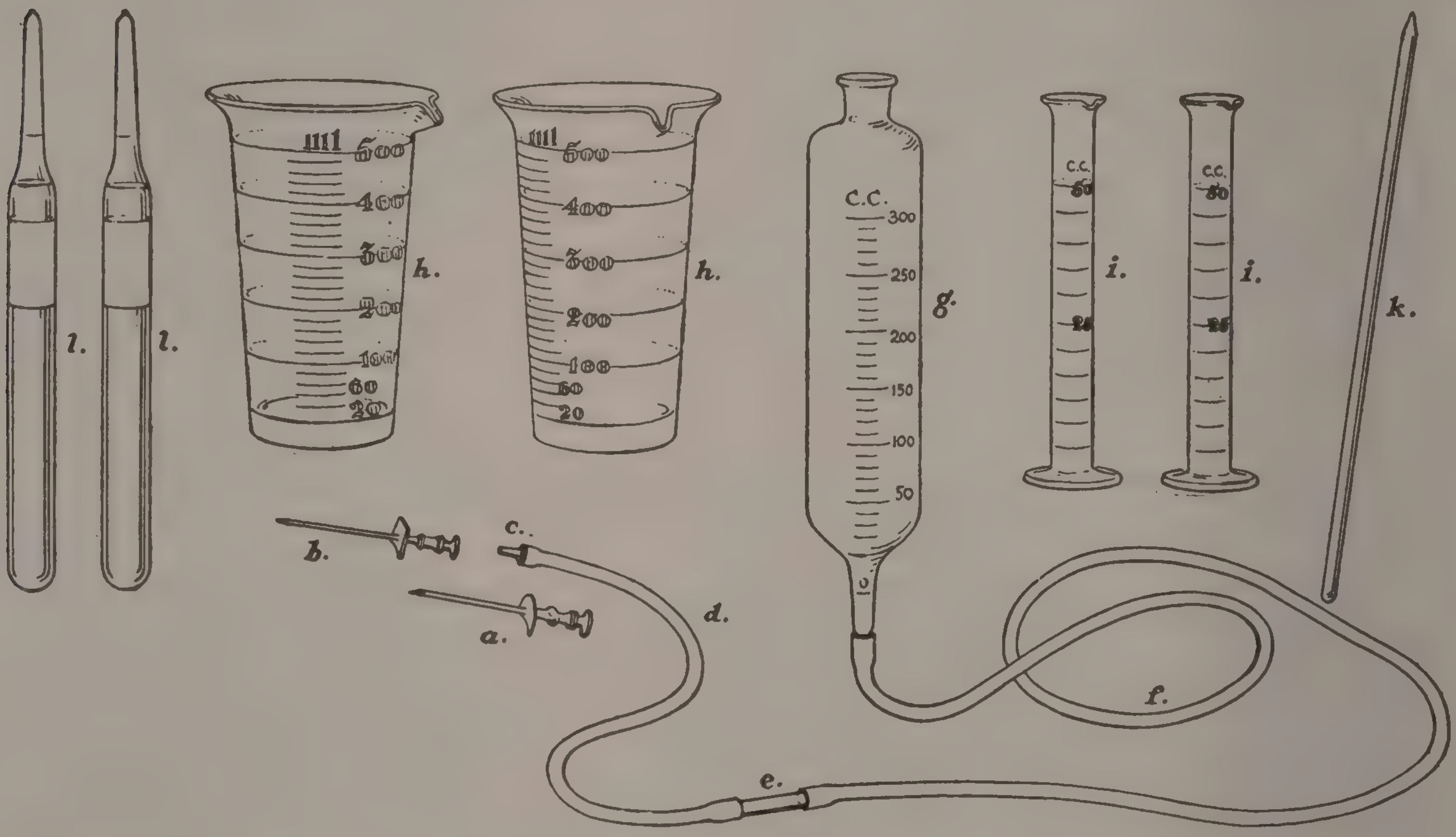

FIG. 6.—APPARATUS FOR CITRATE TRANSFUSION. The objects are self-explanatory except *l*, which are ampules of sodium citrate solution. (Courtesy of Dr. Lewisohn.)

The actual technic of citrate transfusion is extremely simple. The instruments required are sterilized by boiling in plain water. If soda is used (as is the custom in operating rooms for the prevention of rusting), then any soda left in the instruments must be washed out with some plain sterile water or saline solution before they are used. The instruments required are:

2 or more transfusion needles.
2 graduated cylinders of 500 c.c. or 1,000 c.c. capacity.
A stirring rod (any long surgical instrument such as a sound can be used for this purpose).
2 soft rubber tourniquets.
1 100 c.c. graduated cylinder for measuring the sodium citrate solution.
1 bottle of 100 c.c. of sterile 2.5 per cent sodium citrate solution.
1 gravity infusion apparatus, such as is used for saline infusions or in the giving of arsphenamin.

The tip of the infusion apparatus must fit the hilt of the transfusion needles. Occasionally, in cases where the veins are so small that they cannot be punctured by a hollow needle through the skin, it is necessary to also have a set of dissecting instruments for the purpose of exposing the veins. These are:

Scalpel.
Mouse-tooth forceps.
Scissors.
Artery clamps.
Catgut.
Hypodermic syringe.
1 per cent novocain or alypin (without the addition of adrenalin, which makes the veins contract down so that it is difficult to enter them).

In most cases these instruments are not needed, but it is always wise to have them on hand in case they should be required.

The donor should invariably lie down. The chance of his fainting is very much smaller if he does so. His arm need not rest on a table, but more advantageously should hang over the side of the couch or the table on which he lies. His arm is disinfected from the axilla to the wrist, and all the way around, either by scrubbing, or by painting on a not-too-heavy coat of iodin. A sterile towel or a small, specially made bag is thrown around the hand and a sterile towel or sheet is thrown over his shoulder. The tourniquet is applied to the arm as high up as it can be placed in the sterile area, so that, if necessary, it can be changed by the operator.

The application of the tourniquet is simple, but slight errors in the mode of its application are frequently, in the hands of beginners, the cause of a poor flow of blood. The tourniquet must be neither too tight nor too loose. If too tight it cuts off the arterial flow, if too loose it fails to impede the venous return sufficiently. The ready-made tourniquets which are supplied by surgical houses are almost always too heavy. The best tourniquets are simple pieces of very elastic black para rubber tubing of a diameter of about 6 mm. The tourniquet can be fastened with an artery clamp, but it is easier and just as effective to catch it with a simple hitch.

A measured amount of sodium citrate solution is poured into one of the graduated cylinders. It is perhaps best to put in 10 c.c. at the start and then to add 10 c.c. for every addition of 90 c.c. of blood as the blood flows in. But where one is sure that one is going to draw at least 450 c.c. of blood, there is no harm in measuring 50 c.c. of citrate solution beforehand into the cylinder (the fear formerly held that the relatively larger amount of citrate mixed with the first portion of blood might injure it, and produce toxic symptoms, not having been justified in practice).

When the vein of the donor is sufficiently distended, the transfusion needle is introduced into it. This step, like the application of the tourniquet, is so simple that it would hardly seem to require special description. Yet since most of the actual difficulties in transfusion are due to unsatisfactory introduction of the needle, it is worth describing the process in some detail.

The largest needle that the patient's vein will hold should always be used; the larger the needle, the quicker the flow and the less the chance of coagulation. For most male donors, a needle of ten caliber is used. The point of the needle is beveled, but the bevel must not be too long, or the needle is likely to wound the posterior wall of the vein and cause a hematoma. The needle must be extremely sharp and its bore absolutely smooth. It is not necessary to nick the skin first with a scalpel; the needle, if sufficiently sharp, goes through the skin easily. It is usually best not to try to put the needle into the vein with one motion, but to first pierce the skin, and then to feel for the vein with the point of the needle and to push the needle into the vein. The needle can be inserted either directed toward the shoulder or directed toward the hand. It was formerly thought that the insertion with the point directed toward the hand was preferable because this enabled the blood to flow through the needle in the same direction as it has been flowing in the vein. But actually this is of no importance, because the needle is never large enough to obstruct completely the flow of blood from below. It is usually easier to insert the needle pointing upward toward the shoulder.

In introducing the needle the chief guide is not the sense of sight but the sense of touch. For this reason the operator's hands should be disinfected by scrubbing and should be bare; he should not use rubber gloves.

When a trained sense of touch is relied on, it is frequently possible to introduce a needle into a vein which lies so deep that it actually cannot be appreciated by sight at all. When the vein as examined by palpation has any tendency to slip from side to side, it can be made taut by the left thumb of the operator which is made to pull gently on it from below. Care must of course be used not to pull on it so hard as to flatten it out. In some cases where the vein is extremely difficult to enter because of this tendency to slip from side to side, the vein can be fastened to the skin by being pierced transversely with a cambric needle. The transfusion needle is then introduced into the vein about a half inch above the point where it is so transfixed.

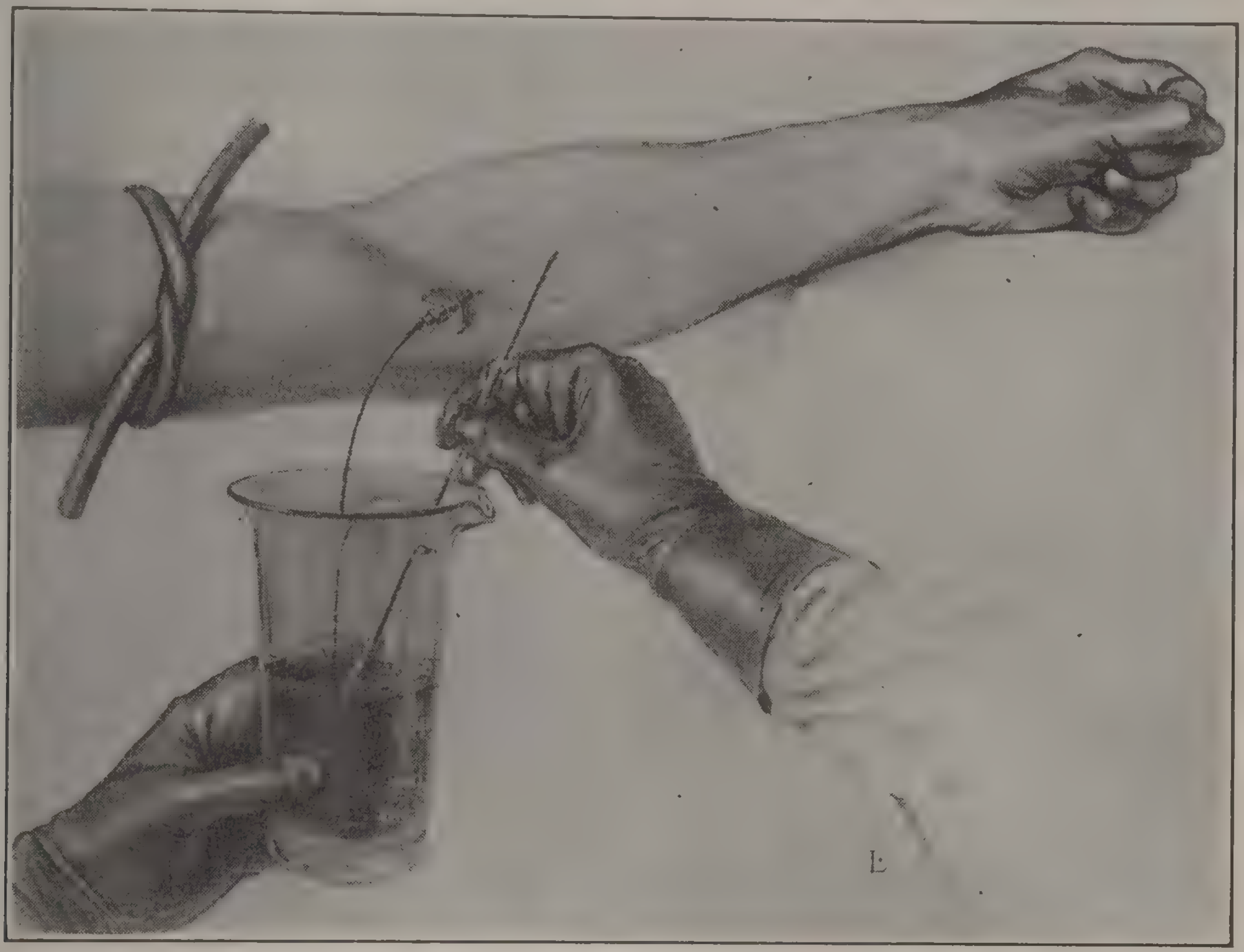

Fig. 7.—The Phlebotomy for Citrate Transfusion. (Courtesy of Dr. Lewisohn.)

The procedure usually requires no local anesthetic, as the pain is momentary and not great. But if desired, a little novocain or alypin can be used in the skin beforehand. This is always advisable indeed in the case of very nervous persons where fear combined with a small amount of pain may produce low blood-pressure or actual collapse.

The needle is introduced without any obturator, so that entrance into the vein is at once announced by a spurt of blood. When this spurt of blood occurs, the needle should not be pushed farther as it is likely to be pushed through the opposite wall of the vein. The large graduated cylinder with the measured out citrate solution is held in such a position as to catch the stream of blood. The blood-citrate mixture is gently stirred, either by an assistant or by the operator himself.

The use of a rubber tube connected to the transfusion needle to conduct the blood into the cylinder is unnecessary, and is probably disadvantageous as it involves a greater amount of friction for the blood, and therefore is more likely to bring about those initial stages of coagulation which are now believed to be partly responsible for certain so-called "transfusion reactions."

If the tourniquet is properly applied the flow of blood is usually good. But the flow of blood can be made more rapid by having the donor intermittently open and close his hand, using in the closing as powerful a muscular contraction as he can. Care must be taken when he does this that he does not dislodge the needle.

When the required amount of blood has been obtained, the tourniquet is first removed, the needle is withdrawn, and gentle pressure is exerted over the vein until there is no more tendency to bleed. The blood obtained can be used immediately. Or, if desired, it can be set aside for as much as several hours (in which case it should be kept at ice-box temperature and warmed to body temperature before use).

The administration of the blood to the patient is an exceedingly simple procedure. The patient's arm is prepared in the same way as the donor's, except that instead of hanging over the edge of the couch or table it should rest on any flat surface. As the patient's blood-pressure is usually lower than that of the donor, the tourniquet usually has to be applied more lightly. A smaller sized transfusion needle can be used (Size 14). It is not necessary or advisable to fill the gravity apparatus with saline solution first. None of the citrated blood should be allowed to flow into the patient until a clear spurt of blood from the patient's vein has shown unmistakably that the transfusion needle is in the proper place. The tourniquet must be removed before the inflow of blood is started.

The apparatus is then held by an assistant higher or lower according as it is desired to give the transfusion rapidly or slowly. It is always wise, even where careful blood tests have been done, to give the first 100 c.c. slowly, taking perhaps five minutes. Then, if no untoward symptoms occur, the remaining blood can be run in as rapidly as desired. In patients in whom there is any dyspnea or cardiac difficulty, the blood should be run in very slowly on account of the danger of dilatation of the right side of the heart.

The technic described is purposely the simplest possible. All of the apparatus needed (except the needles) can be improvised almost anywhere and even the needles can be dispensed with. In emergencies where no transfusion needles are at hand, it is always possible to cut down on the veins and to use some ordinary improvision, such as medicine droppers for canulas. Special forms of apparatus have been introduced, depending on the additional use of suction and of pressure, but they present no marked advantages.

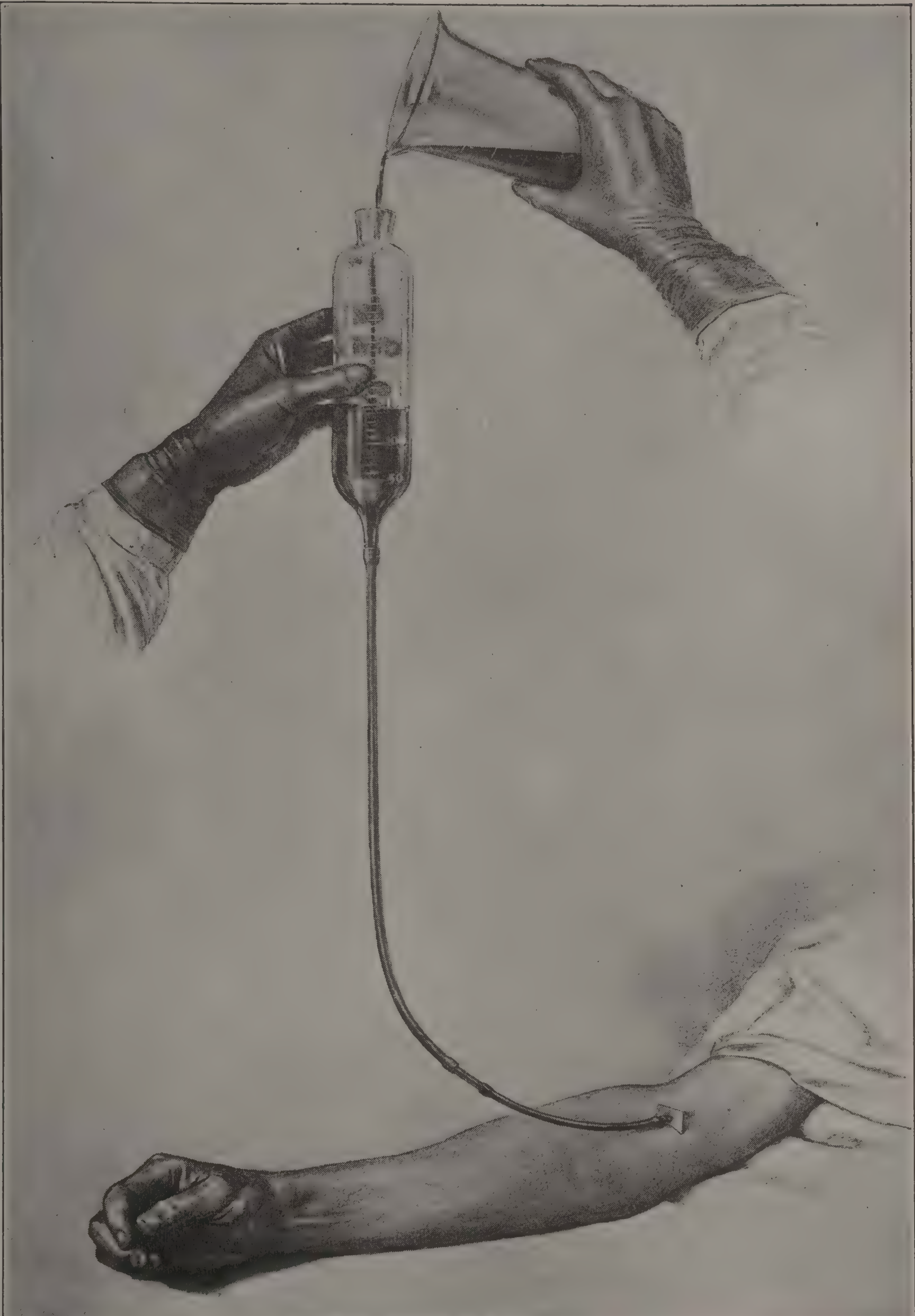

FIG. 8.—THE INFUSION FOR CITRATE TRANSFUSION. (Courtesy of Dr. Lewisohn.)

In infants, and occasionally in poorly developed adults, the veins at the bend of the elbow may be so small that a needle cannot be inserted into them. In such cases often an accessible vein can be found at the inner side of the ankle, or the saphenous vein can be exposed by an incision. This is usually preferable to the use of the external jugular vein.

In young infants in whom the anterior fontanel is still open, the superior longitudinal sinus is often used for transfusion as suggested by Tobler and by Helmholtz. This is entered by inserting the needle to a distance of about a quarter of an inch exactly in the median line at the posterior angle of the anterior fontanel. Provided a free flow of blood is obtained from the needle so introduced, there is no danger of injuring the meninges or the brain. It is very important that the child's head and the needle be held absolutely quiet after the introduction of the needle.

It is desirable but not imperative that the blood should be at body temperature when it enters the body. The blood, even if warm, originally cools off during its course through the gravity tube. The simplest way of warming it is to have the last few inches of the rubber tube through which the blood flows lying in a dish of warm water.

Whole Blood Transfusion

Of the large number of methods proposed for mechanical transfusion of whole blood, I shall describe only one, namely, the Unger stopcock-syringe method, because, after having tried nearly all the others, I believe that it is at present the most neat and certain.

The method requires patient and donor to be lying on adjacent beds or tables either with their heads in the same direction or with their heads in opposite directions. A board or a table of suitable height to which the instrument can be clamped is adjusted between donor and patient. The operator sits on the side of this and his assistant on the other side. The arms are disinfected and a sterile field secured.

Either a nurse must be at hand with bowls of sterile water and sterile saline for rinsing syringes, or an assistant stands by with a can of ether, through a pinhole puncture of whose cap a continuous spray of ether can be kept playing on the glass barrel of the syringe (Elsberg). In this latter case a second syringe should be at hand in case, after all, clotting should occur. In the former case four or five syringes should be provided. Personally I prefer the changing of syringes, and change the syringe regularly after every five barrels full of blood.

Unger's instrument eliminates the difficulties of the Lindeman syringe-canula method. Fundamentally, it is a stopcock, which alternately connects a syringe for blood to the donor and at the same time a syringe with saline to the recipient and then, by a turn of the cock, the syringe with blood to the recipient and the syringe with saline to the donor.

A cock with four outlets is the central part of the instrument. The outlets are as follows:

1. Blood outlet (B). Into this is inserted the tip of a 20 c.c. record syringe (Syr). Through this outlet, by means of the syringe, the blood is aspirated or injected.
2. Saline outlet (S). To this is attached a long piece of rubber tubing, the other end of which has connected to it a syringe for saline solution.

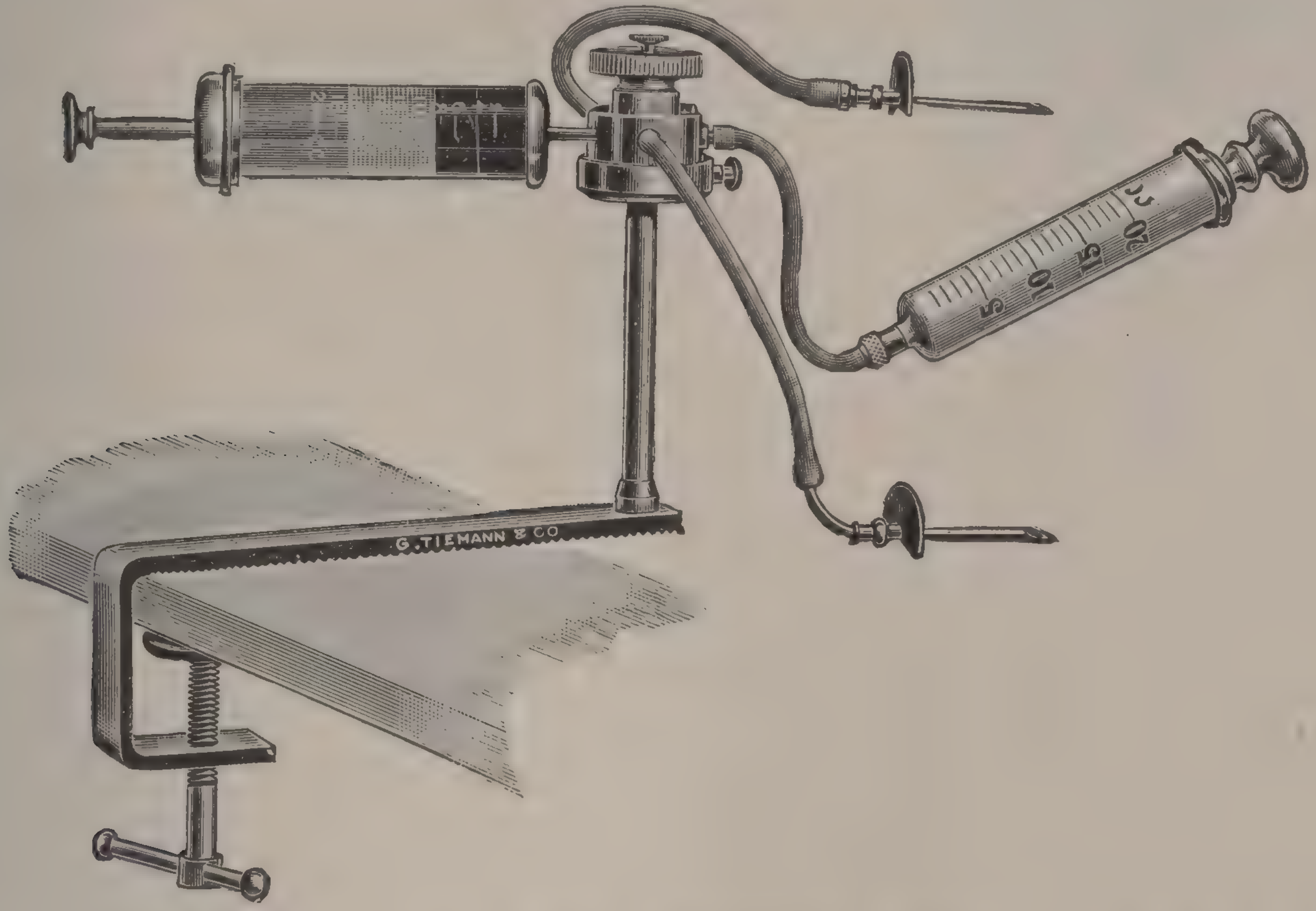

FIG. 9.—THE APPARATUS FOR UNGER TRANSFUSION METHOD. (Courtesy of Geo. Tiemann & Co., New York.)

3 and 4. Recipient's and Donor's outlet (R and D). To each of these is connected a rubber tube which has attached to its other end a metal connecting piece. This, in turn, fits the recipient's and donor's canula.

The cock is so arranged that its rotation allows three possible positions, in two of which two simultaneous circuits exist; in the third no circuit whatever is present. These are:

1. Donor's position (Fig. 10). If the cock be turned toward the donor as far as it will go, a channel between the donor's vein and the record syringe is established for the aspiration of the blood. At the same time, another channel exists, through which saline is injected into the recipient's canula in order to insure its patency.
2. Recipient's position (Fig. 11). If the cock be turned toward the

recipient as far as it will go, again, two channels exist: one through which the blood is injected into the recipient; and one which connects the donor with the saline syringe so that this circuit can be kept patent.

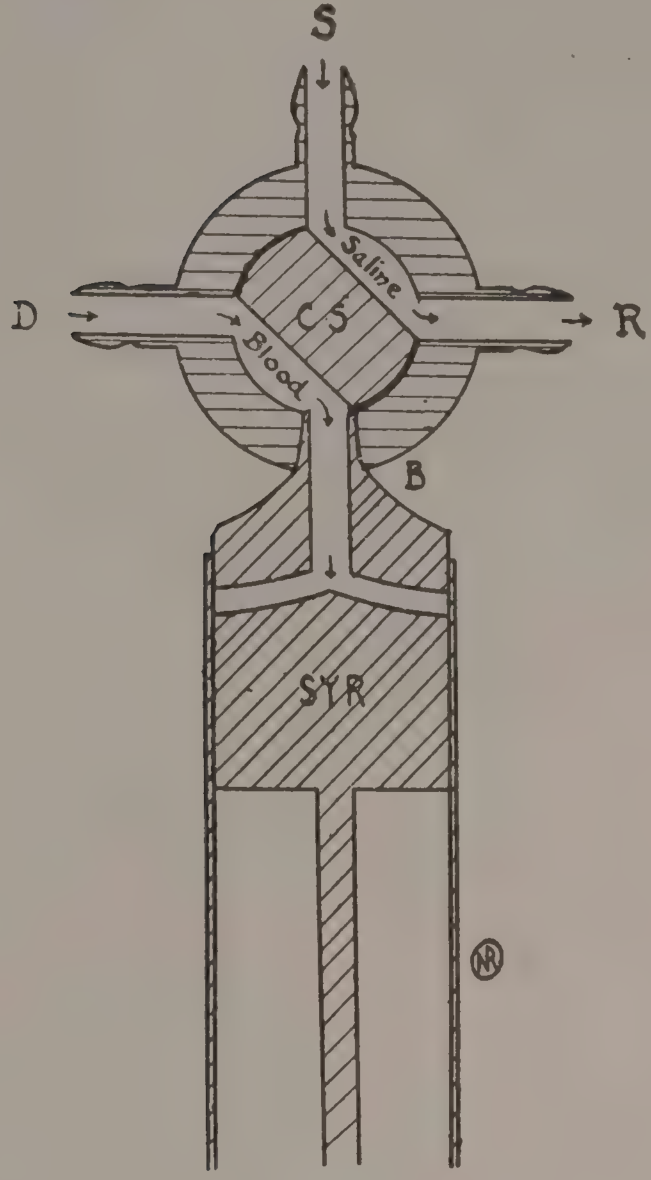

Fig. 10.—Unger Apparatus. Donor's position: D, donor's outlet; B, blood outlet; SYR, blood syringe. Blood passes from donor's vein through D, and out at B into SYR. S, saline outlet; R, recipient's outlet. Saline solution is forced from saline syringe through S, out at R, into recipient's vein. C S, central stopper (rotates through an arc of 90 degrees). (Courtesy of Dr. Unger. From *Journ. Am. Med. Ass.*, lxix, 2159, 1917.)

It is the immediate and continued flushing with saline of that part of the system through which blood is not passing that insures freedom from clotting.

3. Intermediate position. All the outlets are closed off.

The instrument is supported by a mechanical device to hold the cock stationary and to permit its adjustment to various heights.

The stand is fixed to the table. The saline syringe from which all air has been forced out is connected to the saline outlet. The cock is put in the donor's position (Fig. 10) and here also the air is forced out by means of saline solution. The arms of patient and donor with tourniquet in place are adjusted to positions in which accessible veins are easily reached by the canulas attached to the apparatus.

In the recipient's distended vein is inserted a canula, which is then connected to the recipient's outlet. The tourniquet is then removed from the recipient's arm. Saline can be slowly injected into the recipient after the tourniquet on his arm has been removed. Into the donor's vein is inserted a large canula which, as soon as blood spurts from it, is attached to the donor's outlet. Blood immediately runs out of the blood outlet, forcing the air ahead of it. Into this outlet, a record syringe is placed and blood aspirated. When the syringe is filled, the cock is turned into the recipient position (Fig. 11) and the blood injected. Since the assistant is always very slowly injecting saline, he is now flushing the circuit which was used in getting the blood into the syringe. He must remember that more force is needed to inject into the donor than into the patient because the donor's tourniquet has been left in place. As soon as 20 c.c. of blood has been injected, the cock is turned back to the donor's position, and the syringe refilled. This is continued until the desired amount of blood has been transfused. The syringe need not be changed after each injection, but may be refilled until it begins to work with difficulty. Before the syringe is disconnected, the cock should be turned to the intermediate position.

After connections have been made to the canulas: (1) The operator (*a*) aspirates and injects blood, (*b*) changes the syringe when necessary, and (*c*) turns the cock back and forth. (2) The assistant merely slowly forces saline of his syringe. (3) The nurse cleans the record syringes, of which she should have three or four, as fast as they are used, and places a clean one in easy reach of the operator.

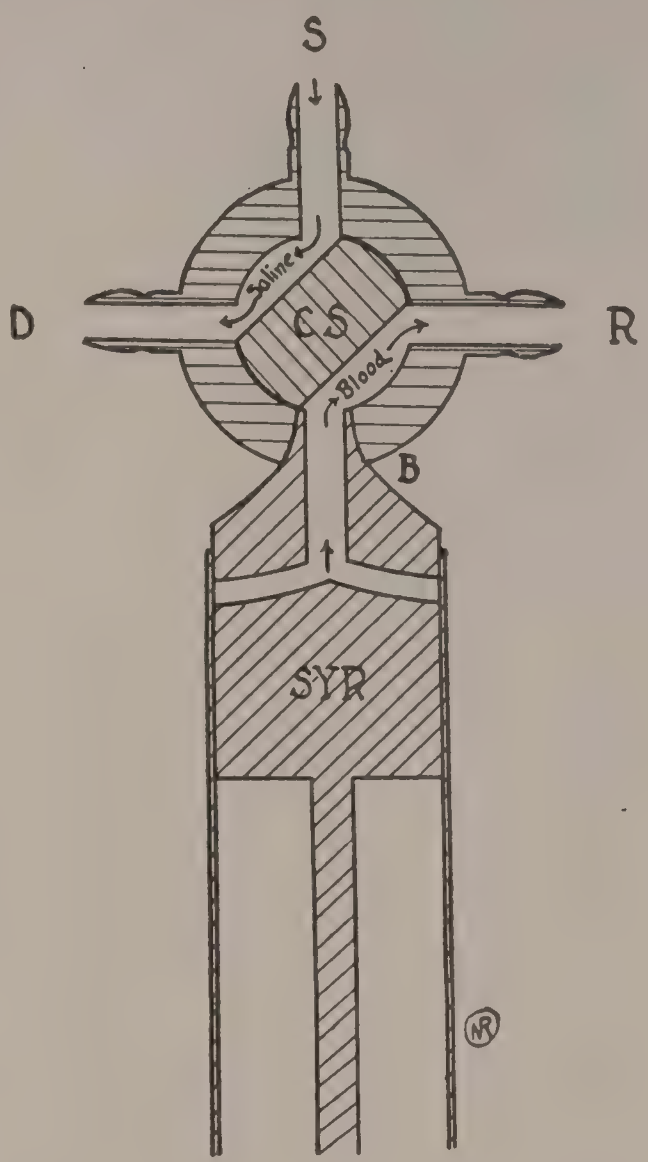

Fig. 11.—Unger Apparatus. Recipient's position: SYR, blood syringe; B, blood outlet; R, recipient's outlet. Blood is forced out of SYR, through B, out at R, into recipient's vein. S, saline outlet; D, donor's outlet. Saline solution is forced from saline syringe through S out at D into donor's vein. C S, central stopper. (Courtesy of Dr. Unger. From *Journ. Am. Med. Ass.*, lxix, 2159, 1917.)

Transfusion Reaction and Advantages and Disadvantages of Sodium Citrate Method

The sodium citrate method possesses most of the advantages that can be demanded of an ideal method of blood transfusion. It is absolutely certain of success; it requires a minimum of apparatus; it can be performed by one operator without any assistance whatever; it does not demand haste; in fact the blood can be kept, if necessary, for hours; and it does not demand any injury of donor or recipient as a rule in the form of an incision.

The only disadvantages that have been claimed against it are: (1) the occurrence of severe chills and febrile reactions following citrate transfusions is said to be greater than following transfusions of whole blood; and (2) the addition of sodium citrate introduces a foreign substance which may have some deleterious influence on the blood transfused. As to the former objection, the frequency and severity of chills, it is not at all yet certain, from the statistical evidence at hand, and I am not completely convinced from an extensive experience with both methods, that the objection is true.

The exact cause of the chills which follow transfusion in a certain proportion of the cases is not known. Probably they are not always due to the same cause. Chills occur (despite statements to the contrary in the literature), after transfusion by direct artery to vein anastomosis, by Lindeman syringe-canula system, by Unger stopcock system, and by the sodium citrate method. I have no experience on this point with the paraffin tubes.

Many considerations make it very probable that some of the chills are related to some obscure change in the blood connected with the preliminary stages of blood coagulation. With all methods of transfusion the chills are less frequent in occurrence, and less severe if they do occur, when the transfusion has gone quickly and smoothly than when it has been difficult or delayed.

There is a possibility that with sodium citrate transfusions some of the unfavorable reactions may be due to samples of sodium citrate whose hydrogen ion concentration (degree of acidity or alkalinity) varies widely from that of the blood (Meleny, Williams). Williams, examining ampules of sodium citrate solution put up by a commercial house for transfusion, found, for example, that some of them presented a considerable degree of alkalinity; that although addition of such citrate to blood might not appreciably alter the reaction of the blood itself (because of the well-buffered character of blood-plasma) nevertheless, the delicate balance of basic and acid radicals in the blood might well be upset to an important degree. It cannot yet be regarded as proved that this is a serious factor, but undoubtedly in the near future attention will have to be given to this point.

I should suggest the adoption of the method proposed by Keynes by which sodium citrate, instead of being kept for use in dissolved form, is kept in the solid form in stoppered bottles each containing 2½ gm. of the salt. These are sterilized at 130° C. and can be kept until wanted. Then the contents of one bottle are shaken into 100 c.c. of sterile warm water in which the citrate dissolves rapidly. A sample of such citrate solution should always be made and tested immediately after the sterilizing process, and only salt whose hydrogen ion concentration is approximately that of blood (pH 7.2) should be accepted. The citrate solution can then be used as described above.

As to the second objection to the use of sodium citrate, that it may injure the transfused blood, there is as yet no evidence that this actually occurs. And there is a considerable volume of clinical evidence that citrated blood is entirely equivalent to blood to which no addition has been made. Ashby has shown that such blood-cells may remain in circulation up to thirty days. And the fear that sodium citrate being an anticoagulant may be injurious in cases of hemorrhagic tendency has turned out to be unwarranted. Actually, as first shown by Weil, citrate used in small doses shortens the coagulation time of the circulating blood.

On the whole I believe that the following attitude is the best one at present. For operators not very familiar with transfusion, in most emergency work, and in routine transfusion of patients whose condition is not very desperate, the sodium citrate method should be used. In an already greatly debilitated patient, on account of the possibility that a more severe chill may be fatal, whole blood transfusion should be preferred provided the operator has the skill to carry it out.

The so-called "transfusion reaction" alluded to has practically an identical character whether it occurs after a citrate or a whole blood transfusion. It never begins at once (unless the transfusion has been exceedingly prolonged), whereas reactions due to blood incompatibility usually begin while the blood is still flowing. Instead it begins a half to one hour after the transfusion. In its worst form it starts in with a severe chill during which the patient may vomit and may be in grave collapse. If the patient's temperature is taken during the chill, it is found to be high (103° to 106° F.). After the chill is over the temperature continues high for from three to forty-eight hours. The urine never contains blood-cells or hemoglobin. There are milder forms of this reaction varying all the way down to a rise in temperature of 1° or 2° without any symptoms whatever.

A transient non-itching urticaria often occurs immediately after transfusion. It seems to have no connection with the occurrence of chills or fever.

The patient or his friends should always be told beforehand of the possibility of the occurrence of the chill; and a nurse or a medical man should always be present or near by until the period during which chills may occur has passed, so that stimulation can be used in case the patient's condition requires it.

Question of How Much Blood To Transfuse

The decision as to the quantity of blood to transfuse cannot be made arbitrarily. No rule can be made which will apply to all cases. On the contrary the question is an important one on which the success of the transfusion often depends, and it requires careful consideration of a number of different factors.

The first consideration in determining the amount of blood that can be transfused is the safety of the donor. To put the answer in terms of concrete experience rather than in the more abstract ones of blood volume, one may say that practically any normal adult can give from 500 c.c. to 700 c.c. of blood without any serious discomfort or after effects whatever, except a mild anemia from which recovery may be expected from one to four months; that most vigorous adult men, especially men weighing 180 pounds or more, can easily give 1,000 c.c. to 1,200 c.c.; and that very large and vigorous men can stand the loss of 1,200 c.c. to 1,600 c.c. Beyond this, one is probably never justified in taking more blood from a single donor.

The second set of considerations has to do with the patient, and depend on:

1. His need for blood.
2. The condition of his heart and arteries.
3. His size and age.

In acute hemorrhage, of course, it is desirable, provided that the hemorrhage has been stopped, to replace as much of the lost blood as possible. Usually the amount lost is not known and as a rule it is much larger than any amount that can safely be given from one donor. Fortunately, however, experience has shown that a considerably smaller amount than the patient has lost generally suffices to restore him to a condition in which he is no longer critically ill. In practice, in these cases, it is usually desirable to give a large transfusion, say 1,000 c.c. for an adult.

On the other hand, in internal hemorrhage, where the bleeding point cannot be directly reached, it is desirable to replace enough of the patient's lost blood to restore him to a condition of safety, but at the same time to avoid raising the blood-pressure to a point which might encourage fresh bleeding. In these cases, therefore, moderate-sized transfusions, perhaps 500 c.c., for an adult are needed. It is better, if necessary, to give several such transfusions at intervals of a day or more than to attempt to restore the patient's condition all at once by a large transfusion.

In shock, likewise, a moderate-sized transfusion is usually indicated because of the fear of dilating the right side of the already enfeebled heart with too large a blood volume.

In general in all conditions in which the patient has not lost blood, however desirable it may be to give a very large transfusion, the amount that can be transfused is usually limited (unless a preliminary phlebotomy is done) by the patient's own blood volume; his circulation only has room for a limited additional amount of blood. Experience has shown that for adults who have not suffered depletion of their body fluids, amounts of blood beyond 1,000 c.c. to 1,200 c.c. frequently cause an uncomfortable feeling of fullness in the head, and some dyspnea.

These symptoms disappear as a rule in a few hours, and it is likely that the circulation either accommodates itself to the new blood volume or manages to concentrate the blood received by the removal of a certain amount of the plasma. That this latter is probably the case appears from the fact that, when the hemoglobin and red blood-cells are carefully observed day by day, it is often found that they show an increase for several days after a transfusion. Exact observations, however, on the blood volume after transfusion are much needed. For these reasons, in chronic wasting conditions, and in the chronic blood diseases, it is usually better to give moderate-sized transfusions, say 600 c.c. to 800 c.c. at intervals, rather than to attempt too much at a single transfusion.

In anemias, an important question is how much rise in the hemoglobin percentage and the red blood-cell count can be expected from a transfusion of a given size. Dr. Libman and I showed years ago that the amount of improvement that may be expected can be calculated with an approximate degree of correctness by a very simple method. It is worth doing this beforehand if only to avoid disappointing the patient or his friends, since the immediate improvement in these cases is less than one might expect, if one had not had experience or if one had not made such calculations.

The method is based on the simple mixture principle. If one were to mix 2 parts of any 100 per cent solution with 3 parts of any 40 per cent solution, the strength of the resulting solution would be easily calculated by adding two times 100 to three times 40 and then dividing the sum by the total number of parts, namely, 5. This would give a 34 per cent solution.

This method of calculation, then, demands that one should know the amount of blood the patient has, as well as the percentage of hemoglobin in it. For rough, practical purposes, since there is at present no satisfactory clinical method of estimating blood volume, the blood volume is calculated as a certain fraction of the patient's weight. Where the patient is very edematous or very emaciated, his previous weight in health can perhaps be more safely taken. The estimates of the ratio of weight of the blood to the weight of the body vary between one-thirteenth and one-nineteenth of the body weight. For the present, we will not err very greatly if we assume one-thirteenth of the body weight to be the usual ratio of blood to body.

Suppose that we have a patient whose hemoglobin is 23 per cent, and whose weight is 130 pounds, he may be estimated as having approximately 10 pounds of blood (1 pound may be taken as approximately 500 c.c.). Suppose that we have a donor whose hemoglobin percentage is 90. If we wish to transfuse 1,000 c.c. of blood we can calculate as follows:

Ten pounds of 23 per cent blood plus 2 pounds of 90 per cent blood will give 12 pounds of blood of what percentage?

$$\begin{array}{rl} 10 \times 23 & 230 \\ 2 \times 90 & 180 \\ \overline{} & \overline{} \\ 12 \text{ into} & 410 = 34 \text{ per cent} \end{array}$$

One can expect, therefore, to raise the patient's hemoglobin by 1,000 c.c. of 90 per cent blood from 23 per cent to 34 per cent. If desired, a similar calculation for red blood-cells can be made. When a preliminary blood-letting is done, of course, the percentage of hemoglobin will be raised proportionately a little more.

With regard to infants and young children the amount of blood that can be transfused should perhaps be taken as roughly in proportion to the ratio of the body weight to that of an adult. Thus, if one had a newborn infant of 5 pounds, and one wished to transfuse an amount which would be equivalent to 1,000 c.c. given to an adult of 150 pounds, one would give one-thirtieth of 1,000 c.c. or approximately 33 c.c. However, in the case of hemorrhage in young infants, one usually can and should go beyond this calculated amount, because in a very small child the loss of a few cubic centimeters of blood is much more serious than it is in an adult, and because we almost never replace the full amount of blood lost in acute hemorrhage in adults by our transfusions. To judge from clinical experience, in infants and young children, it is safe to give at least twice as much blood as one would calculate on the ratio of the body weight to that of an adult.

REFERENCES

A bibliography of over three hundred titles will be found in Geoffrey Keynes' *Blood Transfusion,* Oxford Medical Publications.

CHAPTER X

TECHNIC OF COUNTERIRRITATION AND BLOODLETTING

Joseph C. Roper

COUNTERIRRITATION

Of the value of counterirritation there can be little doubt. It is applied with benefit in the form of hot flaxseed poultices, plain or sprinkled with mustard for the relief of pain as in acute pleurisy or beginning pneumonia, as the regulation hot-water bag in various neuritic or abdominal pains, and in the form of dry or radiant heat or cautery in neuritis. Its beneficial action is probably due to a combination of local congestion and depletion in other parts.

Linseed Poultice.—Linseed meal should be shaken on boiling hot water until of a proper consistency for spreading, spread on thin linen, applied hot and covered with thick flannel or other heat-retaining material. It will keep hot from one-half to two hours, depending on thickness and cover.

Mustard Poultice.—Shake mustard on linseed poultice or stir a small amount of mustard with the poultice.

Mustard Plaster.—Mix thoroughly mustard and flour in equal proportions for an adult or in proportions of one part mustard to four or six parts of flour for a child. Moisten with warm (not hot) water. Hot water liberates the irritating oil which should be liberated only by the warmth of the body. Spread on gauze and apply and keep on until skin underneath is bright red—about ten to twenty minutes for a child and twenty minutes or more for an adult. Do not blister.

Stupes.—Flannel is wrung out of very hot water, plain or with turpentine, 1 tablespoonful to a pint of boiling water. Coarse toweling fastened between two sticks is usually used for wringing. Stuping is most useful for abdominal distention, is kept up continually for fifteen to twenty minutes and repeated p. r. n.

Mustard Bath.—Prepared by mixing with warm water and adding to bath in proportion of 1 ounce of mustard to 4 gallons of water; or mustard may be put in an impromptu cloth bag and suspended in water.

Continuous Bath for Burns.—One-half saturated boric acid solution (saturation point one to thirty-two), temperature 100°, or 5 per cent of sodium bicarbonate may be used.

Active Hyperemia.—Electric heat or gas flame heat may be employed. Many types of apparatus are on the market. They consist essentially of a box divided into hinged upper and lower portions with holes to admit the member. The holes are surrounded by felt cuffs which strap on the arm or leg. Heat is furnished by electric lamps or admitted through a pipe at one end of which burns a gas flame. The other end leads into the box. A vent is provided above and a thermometer is passed through the top into the chamber. A temperature of from 150° to 250° may be reached but discomfort should be avoided. The member treated is wrapped lightly in protective covering and heat is continued for from thirty to sixty minutes. Cooling should be gradual, the limb remaining in the box for a time after the current or flame has been turned off, and not removed until the temperature has been materially reduced.

Dry Cupping.—Dry cupping finds its greatest usefulness in the relief of edema of the lungs.

Cupping glasses are round-edged thick glass jars used for relieving congestion of underlying parts. The cups may be obtained plain or equipped with suction bulbs. In an emergency thick smooth-lipped small or large glasses may be used. These should be carefully dried out and swabbed or rinsed with alcohol, the excess being drained off. The alcohol remaining is ignited from an alcohol lamp or torch and the cup quickly applied to the skin. The burning alcohol exhausts the air and the vacuum formed causes the skin to bulge up into the glass. The capillaries fill with blood and when the vacuum is exhausted the cup loosens. If the cups do not fall off, the vacuum is relieved by pressing down the skin at the edge and allowing air to enter.

BLOODLETTING

Venesection.—Venesection is indicated for quick reduction of high blood-pressure as in cerebral hemorrhage due to hypertension, for the relief of an engorged area or organ as in pulmonary edema, congested liver, or an enlarged right heart and for removal of circulatory poisons or toxins, as in illuminating gas poisoning and uremic convulsions. The technic consists in compressing the upper arm by a bandage or tourniquet tight enough to obstruct the venous but not the arterial flow, exposing one of the superficial veins at the elbow by an incision through the skin and incising the vein transversely, being careful not to divide it completely. Where the veins are large and easily entered, sufficient blood may be removed through a large aspirating needle plunged directly through the skin into the vein. The amount withdrawn varies with the indication and reaction, but is usually from 200 to 500 c. c. from an adult and from 50 to 100 c. c. from a child. The work is best done in a semi-erect position. Appearance, pulse, and blood-pressure should be used as guides in deciding when sufficient blood has been withdrawn.

Wet Cups—*Technic.*—A dry cup is first applied as previously described. Immediately after removing the cup parallel incisions about an inch apart are made through the skin only over the swollen area. The cup is reapplied at once and from 1 to 3 drams of blood removed. The writer must confess to never having seen wet cups applied in New York City, although hospital patients, mostly foreign born, not infrequently are seen with scars from former wet cupping. The utility of the procedure is doubtful, and as satisfactory results may probably be obtained by counterirritation.

Leeching.—To one trained in a metropolitan hospital in the modern conception of disease the application of leeches for local bloodletting seems a peculiarly futile procedure. The therapeutic effect must be almost nil. In conditions for which it is often recommended, as in ecchymosis about the eye, it has no effect on the ecchymosis and adds another injury to the already existing one. The wound often continues to bleed after the leech has quit and occasionally the bleeding must be controlled by a suture. A small scar usually results.

If one feels a leech must be used, it may be applied by means of a test tube in which it has been placed with the small end out. If it has been out of water an hour or more it will take hold more readily. A skin puncture may help. It will usually drop off when full and, if it does not, application of strong salt solution will help in its removal.

CHAPTER XI

PRINCIPLES AND TECHNIC OF THERAPEUTIC PROCEDURES IN GASTRO-ENTEROLOGY

Arthur L. Holland

Stomach Tube.—About fifty years ago Kussmaul devised a tube for the study of gastric digestion and for treatment. Very little experimental work had been done in this field prior to this. The ingenious device soon became popular and it is not difficult to understand its hold on the imagination of that time or since. To deny that the invention has been of great benefit would be aside from the facts. Much valuable information has been gained through the research and experiments made possible by it. The work of Pavlow and others, through animal experimentation, has perhaps resulted in more accurate information as to the physiology of digestion, but the stomach tube has earned a prominent place among the medical and surgical instruments devised in the last century. And even now it is far from having retired to a shelf in the museum. But, so far as gastric digestion is concerned, its possibilities in experimental research seem long since to have been exhausted.

Duodenal Tube.—In modified form, as the duodenal tube, it is still being used for experimental purposes farther along in the alimentary canal. As a means of diagnosis, the stomach tube has not entirely maintained the place that the early extravagant predictions had promised for it. It remains a useful aid in diagnosis, but quite stripped of value as a decided factor. As a therapeutic agent the stomach tube has had a more than checkered career. Its popularity in this rôle continued for many years. It was thought a panacea for nearly all gastric ills. If we have been somewhat disappointed in the stomach tube in diagnosis, in treatment it is little used except in emergencies, or rarely for lavage, serving as a temporary substitute for surgery in obstruction. Quite recently the duodenal tube has been employed in attempts to drain the gall-bladder in the interests of both diagnosis and treatment and for purposes of transintestinal lavage. This will be discussed later.

Any new method introduced into medicine is apt to attract, by its novelty or other appeal, workers from general medicine who become devotees—specialists, in other words—and when in medicine any number of men narrow their endeavors to a specialty, it usually results in a multiplication of diagnostic methods, the designing of new instruments, or the modification of old ones; the pharmacopeia, official and otherwise, is burdened with additional drugs, much as the dictionary is expanded to accommodate an enlarged and altered terminology. These are some of the embarrassments that the stomach tube has brought to medicine; hence this preamble in which this device has been discussed at such length.

This chapter will deal so far as possible with those special methods, instruments and appliances that have come into use as the result of the intensive study that has been given to the diseases of digestion since the introduction of the stomach tube; but only those procedures that have survived in this critical and sophisticated decade, and are now in use by those of undoubted authority, will be presented. It seems to the writer that success in treating these disorders depends largely upon the care with which the cases are studied from a diagnostic standpoint; that, where surgery is not indicated, the treatment largely resolves into a regulation of the patient's hygiene, both mental and physical.

Review of Drugs.—Most drugs have fallen from their high places; even hydrochloric acid is under suspicion of being little more than a placebo.

Hydrochloric Acid.—The benefit derived from the use of hydrochloric acid in some cases comes about probably through its stimulating action on the pyloric valve, which, in the low acid states and achylia, tends to relax with a more or less precipitate emptying of the organ. The small amount of acid usually given could hardly have much digestive action and it cannot be proved in practice that, as a hormone, it stimulates the acid cells to any degree, as the natural appetite juice does, as was shown by Pavlow and Edikins.

Pepsin, Pancreatin, Diastase.—The preparations of the ferments, pepsin and pancreatin, and the starch converter, diastase, will undoubtedly act in a test tube, and these preparations probably do have some mild digestive action within the stomach. But the practical results are not very good and it is doubtful if any hormonic action ever results from their employment. Perhaps, as time goes on, the endocrinologists will discover in their researches means for controlling somewhat the digestive secretions, but, except where the endocrine system is itself deranged in one way or another, the glandular preparations suggested for this purpose would seem both innoxious and inefficient.

Nux Vomica.—Nux vomica has degenerated into a "non-alcoholic cocktail," an appetizer, its effect on the gastric digestion lasting, it is thought, only from meal to meal. Tonics and bitters generally have gone "by the board" along with the nervines and reconstructants of not long ago.

Cathartics.—We still have the various cathartics and laxatives and even now use them too promiscuously and with little regard for our knowledge of their true action.

Cholagogues, Calomel.—Most of us have long since given over calomel as a cholagogue; in fact, cholagogues as a class, we fear, have fooled us too long. Irritants they certainly are and thus excitants of peristalsis. But that they have any direct stimulating effect on the hepatic cells or the gall-bladder is doubtful.

Bile Salts.—If bile salts would produce results in one case in a hundred we might feel encouraged to persist in their use, as the theory of their action is not so illogical. But we rarely if ever see any effect, except where the proprietary medicine man adds cascara, phenolphthalein, or other mild laxatives to his preparations of bile salts.

Castor Oil.—In castor oil we have a tried and reliable, if somewhat disagreeable, cathartic; there is nothing else that will quite take its place.

Saline Laxatives.—Saline laxatives are not often of value in gastrointestinal cases except for temporary use and perhaps for short courses of treatment similar to the Carlsbad temporizing treatment for gall-bladder disease and such ailments.

Vegetable Laxatives; Phenolphthalein.—Cascara, rhubarb, podophyllum, senna and all that class of vegetable laxatives are of limited use in overcoming the constipation incident to acute and subacute disease, and in constitutional states where the motor and secretory functions of the intestines are known to be impaired. But they are rapidly proving more harmful than otherwise in the treatment of chronic constipation. The same is true of phenolphthalein.

Liquid Petrolatum.—Liquid petrolatum (mineral oil) is invaluable in the treatment of constipation and obstipation, particularly the latter condition. It stimulates peristalsis but little; hence it is non-irritating and can be used over long periods of time. In the colon it seems to act somewhat as a protection to inflamed areas, and its incorporation in the fecal mass tends to soften the consistence, thus preventing accumulation in pockets. It is usually given in larger doses than is necessary; ½ an ounce at bedtime on alternate nights will frequently act better than a larger dose administered every night.

Agar-agar.—Agar-agar is even more valuable than liquid petrolatum; its water-carrying and bulk-forming qualities render it an ideal adjuvant to a bulky, laxative diet.

Eserin Salicylate, Pituitrin, Adrenalin.—Eserin salicylate, pituitrin and adrenalin may rarely be of some use in postoperative intestinal difficulties and in other forms of acute intestinal obstruction that appear to be dependent on toxic, paretic or reflex causes.

Sedatives and Narcotics.—In the sedatives and narcotics we have drugs that can be depended upon to act—two-edged weapons and always dangerous, but nevertheless useful on occasions and sometimes, though rarely, life-savers. There is in medicine no problem requiring finer judgment than in the prescribing or withholding of sedatives and narcotics in gastro-intestinal emergencies or in their use in chronic or subacute abdominal disease.

Opium, Bromids, Chloral, Luminal.—Opium and its derivatives hold first place. As sedatives, the bromids, chloral and luminal are exceedingly useful, if carefully controlled in appropriate cases.

Carminatives.—The carminatives of the old pharmacopeia may be excellent placebos, but that they have any other effect is hard to demonstrate; and yet, the writer must confess that he not infrequently resorts to the much discredited valerian in functional irritability of the colon.

Belladonna.—Belladonna in reflex spasm throughout the gastro-intestinal tract is undoubtedly of some value, but one must use it to full physiological effect, and even then it frequently fails or causes too much constitutional disturbance because of idiosyncrasies. In spasm of the esophagus and cardia, its effect is most marked. Pylorospasm does not yield quite so readily to its relaxing effect, and spasticity of the colon depends on so many and various reflex causes and is usually of such a chronic habit, that it promises very little here. Since we suspect that the gastric secretory irregularities in ulcer of the stomach and duodenum are secondary and not the cause of the lesions, it would seem not entirely logical to expect too much permanent relief from its supposed inhibiting effect on the gastric secretory apparatus, and in the writer's experiences, at least, this has proved to be the case.

Local Anesthetics; Cocain, Novocain, Orthoform, Anesthesin.—The action of the local anesthetics is so transitory that they are of doubtful value. In acute painful inflammatory disease of the esophagus, cocain and novocain are useful. The action of orthoform and anesthesin in these cases has not been so marked as it seems to be in rectal practice. In some cases of gastric hyperesthesia these synthetics combined with bismuth have given some temporary relief. The writer has used them as a prophylactic for seasickness, with apparently good results, and the reflex vomiting of pregnancy has occasionally responded somewhat to their use. In gastric carcinoma local anesthetics should at least be given a trial for the incessant soreness so frequently complained of in these distressing cases.

Carbolic Acid, Tr. Iodin, Creosote.—Minute doses of carbolic acid will not infrequently relieve for a time gastric hyperesthesia and the vomiting incident to this condition. Tincture of iodin may be used in the same manner, and creosote is occasionally of value.

Alkalis.—Of all the drugs used in gastro-intestinal practice the alkalis are probably the most popular, and when properly administered offer the most relief for the symptoms caused by hyperacidity and gastric peristaltic unrest which is so constant an accompaniment of hyperacidity. The writer has confirmed the observations of those investigators who have repeatedly asserted that it is rarely the direct action of the high acid chyme on the inflammatory lesions in the stomach and duodenum which is responsible for the epigastric distress common to such lesions. The alkalis neutralize or at least reduce the acidity and in this way relieve the motor irritability which seems to be the immediate cause of this pain; a fine distinction, perhaps, but one which explains the relief that alkalis so often afford when the acid values are relatively low. There is a long list to select from, but the writer has narrowed his use to one combination which has proved satisfactory in routine practice, that is, equal parts by weight of magnesium carbonate (light), sodium bicarbonate and bismuth subcarbonate; a teaspoonful of this combination is taken in water one hour after a meal, or at the time the acid curve is habitually at its height, as shown by fractional gastric analysis.

Rhubarb and Soda.—The officinal mixture of rhubarb and soda, frequently used in combination with nux vomica and cascara, is the most popular placebo used in clinic practice. It is quite all right for many of the functional disturbances, if one is willing to temporize in these cases. But it seems too bad to have to resort to this practice when, by a regulation of the patient's hygiene, he may be straightened out, or, by a frank confession that a diagnosis has not been made, the patient is released to seek aid of those who will take the trouble properly to investigate his case.

Bismuth.—Bismuth alone or in combination can hardly be dispensed with in treating diseases of the stomach and intestines. In the stomach it is something of an antacid and the mechanical protection it affords inflamed, raw and ulcerated mucous membranes makes of it a valuable agent. In the intestines these properties can also be utilized, but as it passes along the tube its incorporation in the intestinal contents renders it of less use in this mechanical way. But, here, its slightly astringent action is of value when given in large doses. It would seem to have some slight antibacterial action; at least the stools become slightly less putrefactive when it is given. The ideal inorganic intestinal antiseptic, however, is yet to be discovered; none that we know of has proved of any great value.

Bacillus Acidophilus, Bacillus Bulgaricus.—In the action of Bacillus acidophilus and Bacillus bulgaricus we have also been disappointed. The lactose with which these products are usually administered, it is thought, is the agent responsible for the change in flora that can be detected in the stools of patients thus treated. A manipulation of the diet, however, is much the better way to accomplish this result. Rettger and Cheplin have recently found that the Bacillus acidophilus when given in milk cultures in very large amounts can be depended upon to effect a change in flora. They have found that lactose in large doses will also have this effect. What the ultimate practical results of this plan of treatment will be remains to be determined; it gives promise of something more interesting than has the administration of Bacillus acidophilus in tablet form [1] or as broth cultures.

Tannic Acid.—Tannic acid, as such, is not often in these days employed as an astringent, but tannigen, tannoform and tannalbin act efficiently in this manner.

Silver Salts.—The various silver salts are now seldom given by mouth but are still used in flushes in ulcerative disease of the colon.

Ipecac.—In amebic dysentery and other protozoal diseases, emetin has produced results, but the writer has come to regard ipecac (in enteric capsules) as somewhat more reliable. In tropical sprew, thymol should be given a trial as it not infrequently gives relief.

Vermifuges.—The vermifuges such as male fern, pelletierin, santonin, etc., have not been improved upon in recent years.

In this rather sketchy review of the drugs used in modern gastrointestinal practice mention has not been made of those drugs which act on the organs and tissues not actually of the digestive system—those of the respiration, circulation and urinary systems. And this is a serious omission when we consider how sympathetic the stomach and intestines are to the troubles of their neighbors. These matters, however, are adequately dealt with elsewhere by those more competent than the writer of this chapter.

From the foregoing it can be seen that the writer, if not a therapeutic nihilist, is at least not an enthusiastic dispenser of drugs. He feels that his success in treating digestive diseases has been in proportion to the care with which he has employed the diagnostic equipment at his disposal, in an effort to arrive at an understanding of the causes responsible for the various organic changes or functional irregularities presented, attacking "at the source" when the cause is ascertainable and by the simplest practical means available, correcting so far as possible the disturbances underlying the symptoms complained of.

Hygiene.—This kind of practice, therefore, has largely to do with hygiene—hygiene in a very broad sense, for it must necessarily include some features of applied psychology as well as the hygiene for organically normal and for sick bodies.

Neuroses.—A large majority of the patients who seek aid for gastrointestinal complaints are organically sound, their symptoms being the result of functional disturbances—neuroses. In not a few of these cases the trouble has no other basis than in misconceptions of one kind or another due largely to faulty education or cherished traditions. Many of the patients are temperamentally neurotic; in fact, the neurologist and gastro-enterologist might exchange clinics and both feel quite at home. But it is unsafe to make a diagnosis of "gastric neurosis" in a case and to proceed with treatment, until it is proved by careful study that there is no organic change responsible for the symptoms. When this has been done the most difficult part of the work still lies ahead. There must always be a cause, and to search this out and apply the appropriate *psychotherapy* is a serious tax upon the best-equipped and cultured of physicians.

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[1] In my experience Bacillus acidophilus is of no value in tablet form.—Editor.

Freud.—Freud and those of his school would have us believe that the cause of most neuroses lies in outraged, thwarted or repressed sex instinct. The writer cannot entirely square this with his experience in clinics or in private practice. The influence of race, education, structural handicaps and maladjustments to environment are too often of etiologic importance in such cases to be ignored.

Neurasthenia.—Neurasthenia may occasionally have its origin in emotional shocks or strains, in some way connected with the sex life of the individual; remote perhaps, even antedating adolescence, but surely not all neurasthenics "arrive" in this manner. In many such cases, in a majority, in fact, there are fairly tangible reasons for the warped mentality and it becomes our office to search these out. If one is not trained to follow out this line of investigation and treatment according to the approved methods of the rational analysts, one can at least tactfully expose and explain away many of the misconceptions commonly entertained by these patients: for instance, that belching is of any significance other than a habit, an indication of the individual's temperamental status; that some gas is normally contained in the stomach and intestines and that its presence is made manifest by the peristaltic unrest secondary to emotional disturbances such as fear, fatigue or food phobias, rather than that it is due to excessive fermentation and putrefaction.

Food Phobias.—In the food phobias and supposed idiosyncrasies to special articles of diet there is more material to discuss than the allotted space allows. It is surprising how few of the many individuals who think they are especially sensitive to some article of diet, such as milk, eggs, fish or fruits, or, in fact, any of the food elements, have any real intolerance for them, and they, as a rule, relinquish these fixed ideas reluctantly. Indeed, they are apt to be proud of their "distinguishing idiosyncrasies," and one's patience is sorely tried endeavoring to correct these false ideas. The uneducated can usually be managed rather more successfully in this respect than the pampered patients of higher mentality. They accept the arbitrary statements of their medical advisers with less question and are usually more loyal, while the better educated must needs be convinced by something more than the bare statements of one medical man when they recall that all their lives their physicians have accepted as facts these peculiarities and have steered their dietetic courses accordingly. One method for convincing and curing those so obsessed is to accept tactfully such a premise as proved, and to administer systematically minute quantities of the food in question, gradually increasing it each day. It may even be given in capsule form at first for its psychological effect. As a matter of fact, this is not an illogical procedure, even in the cure of those who are truly sensitive. But this course has a serious drawback in that the attention of the patient is focused with increased intensity on the particular article that is being tried. In many cases it is, perhaps, better not to compromise but to insist on the food in question being taken in normal amounts, until by personal observation the physician can be sure that there is a real intolerance. And this is not always so easy as it sounds. The subconscious reaction to fixed ideas can become manifest in unexplained and bizarre phenomena. An urticaria, for instance, has been known to develop following the taking of some dish that the patient thought contained some element of food that had always so acted, but which as a matter of fact had not included this article. Vomiting and even more serious symptoms have likewise been induced as a response to this trick.

Mental Anorexia.—There is another class for the neurotic individual whose loss of appetite for all food sometimes proves difficult to understand and to relieve. This may result from shocks, grief or worries, or prolonged dieting, or it may occur in consequence of the elimination from the diet of one article after another, until there is little left that the sufferer does not consider harmful to him. The lack of appetite in these cases is entirely psychic and that it has no organic reason does not render it less serious. Dejerine and his disciple, Gauckler, class these cases as primary and secondary mental anorexia and cite many cases to show that they may result seriously if not fatally. These cases do not usually respond to medication. Here, forced feeding is indicated in which cream and lactose, or other such food elements that can be easily swallowed, may help to break up a vicious circle in which undernourishment holds an important place. But efficient psychotherapeutic management is also essential. Change in environment and in interests help not a few, while the suggestion to such a sufferer that his trouble is mental may add some shock and cause untoward reaction; a gradual education, combined with the exercise of what powers of suggestion the physician may possess, is not infrequently followed by gratifying results.

Mucous Colitis, a Neurosis.—This plan of campaign is perhaps the best for treating most of the gastro-intestinal neuroses. Explaining to a patient, for instance, in non-technical language that mucous colitis is usually the expression of a secretory neurosis, that the mucus evacuated is not unlike tears, in that it is secreted in response to emotions rather than that it is caused by some organic inflammatory change. The banishing of this fear alone may help considerably, and this allaying of fear holds good also in the management of constipation which is so largely dependent upon misconceptions of one kind or another.

Constipation.—Faulty habits and laziness are usually the starting point in constipation, but the condition is often maintained and a cure prevented by the patient's fear of the consequences of constipation which have been ground into his consciousness from his earliest youth. Indeed he inherits this phobia from far back, for was it not Hippocrates himself who gave as his rule for health, "Keep your head cool, your feet warm and your bowels open!" At least this formula came to us from some ancient source and it is a question of whether it has not done more harm than good. Not that regular bowel movements are not essential, but because the constant stressing of this fact has led to the widespread habit of drugging, and it is this meddling in Nature's business that has caused infinitely more trouble than occasional lapses in the bowel function. In functional constipation, which, after all, is usually obstipation, if the diet is properly arranged and, when necessary, the pelvic colon is gently relieved of its accumulation by means of a small low enema either of oil or of saline solution, and all laxatives are discontinued, the patient will usually gradually recover, but there is small chance for a cure so long as the patient, through fear, takes laxatives surreptitiously or otherwise.

Suggestive Treatment.—Suggestive treatment is not to be confined entirely to the treating of the neuroses. There are functional disturbances, and even organic diseases, in which it can be employed to good advantage. The recent vogue and apparent success of the many popular faith cures is witness to this, but the large number of unfortunates who have become the victims of ignorant healers is alone good reason for qualified physicians to add this subtle weapon to their armamentarium. And there is no field in medicine where suggestion can be of greater use than in the treatment of gastro-intestinal disease. If, after a painstaking investigation, a doctor can tell his patient with confidence that he is organically sound, he is surely in a better position to use rational psychotherapeutic measures for the further benefit of his patient than is the healer who, relying on the law of averages, hopes that his subject is one of those of a relatively small percentage of individuals that he can reach by his limited and inelastic formulæ. Or, having discovered some irregularity or lesion, even the name of which is a terror to the patient, the physician can, by an exercise of kindly and tactful suggestion, allay fear and so adjust the patient to conditions that a coöperation is established which can only result happily; or by these tactics at least avert to some extent the anguish that the knowledge of impaired health brings to most people.

INDICATIONS FOR SURGICAL TREATMENT IN GASTRO-INTESTINAL DISEASES

In the treatment of gastro-intestinal diseases, the question of surgical interference is raised more often than in any other practice, excepting perhaps gynecology.

While a discussion of the relative merits of surgical and medical procedures in these abdominal problems does not come entirely within the scope of this chapter, the writer feels that, as the medical man is usually given the responsibility of deciding in these matters, he should be equipped to render his opinions in these cases with authority based on a knowledge of the underlying principles involved, and that some references to these principles are, therefore, not entirely out of place.

There should be no serious conflict between the medical and surgical opinions on these questions; fortunately, the surgeon and internist are rapidly getting closer together in these matters; indeed the internist in these days is very apt to complain of the surgeon's conservatism and the surgeon of the internist's lack of restraint in ordering operations.

The indications for surgery should be definite and based on the probability that it is the better and safer procedure in the individual case, not because the particular disease the patient suffers from is usually considered a surgical problem, but because the surgeon can accomplish something in that case that medical management has failed to do, or for which it offers less promise.

Acute Surgical Diseases of Abdomen.—This discussion will not include the acute surgical diseases of the abdomen, those "catastrophes" with which we are not infrequently called upon to deal—such as perforating ulcer, acute suppurating appendicitis, intestinal obstruction, mesenteric thrombosis, strangulated intestine, etc.—but rather those chronic disorders that can be grouped and ambiguously called "indigestion"; in other words, gastric and duodenal ulcer, chronic gall-bladder disease and chronic appendicitis. Gastric cancer will also be considered.

The time has long since passed when a mere diagnosis in such cases, no matter how positively made, will suffice as an indication for surgical interference. The problems are many and complicated.

Fluoroscope and X-ray Films in Diagnosis.—The diagnosis of gastric and duodenal ulcer can now be made with a considerable degree of positiveness. The X-ray, particularly the fluoroscope, has rendered this possible. Not only is a correct diagnosis usually attainable, but the experienced fluoroscopist is also able to determine the exact location, the size of the lesion and the effect it exerts on the adjacent tissues. By studying such lesions at regular intervals during a course of treatment, changes occurring in the lesion and in the motor mechanism and other functions of the organ are comparatively easy to demonstrate. Such observations carried on postoperatively are a most valuable check on the surgeons.

Surgery Indicated in Gastric Ulcer.—While the results of the medical management of ulcer of the stomach compare favorably with those of surgery, an exploratory operation, at least, is indicated in all gastric ulcer cases. In justification for this dogmatic ruling it is only necessary to point out that while the X-ray, in a large percentage of cases, is effective in differentiating simple ulcer from carcinomatous ulcer, we can never be perfectly sure. Nor can we say that a simple ulcer will not later become cancerous. The blood count, gastric analysis and other tests are apt to fail us when we most need help. In the past year two individuals under thirty years of age, suffering from carcinoma of the stomach, were admitted to the New York Hospital. Gastric carcinoma is not always distinguished by low or absent free hydrochloric acid.

Types of Operations in Gastric Ulcer.—The type of operation in ulcer of the stomach naturally depends on the extent of the lesion and its location. Excision, when possible, either by knife or cautery, should be the rule. A sleeve resection for those ulcers in the pars media where extensive adhesions do not complicate seems to give the best results and is not so often followed by hour-glass contractions. But these cases are not too frequent and the cautery or ordinary knife resections are most often used. On physiological grounds alone, a gastro-enterostomy in these cases is not indicated. There is seldom any great elevation of the acid curve in these gastric cases, and any change in the acid values brought about through a gastro-enterostomy, with its rapid emptying and the addition of bile to the stomach contents, does not seem to compensate for the unpleasant symptoms that frequently follow this procedure, when it is not indicated because of obstruction.

Gastro-enterostomy in Gastric Ulcer.—It is a safe rule to follow in such cases, that if such an ulcer can be shown to interfere persistently with motility either through a reflex pylorospasm or spasm in any zone of the organ, a gastro-enterostomy is indicated, but one must be sure that such embarrassment is more or less permanent. This requires close and careful study before operation.

Prepyloric Ulcer.—In the prepyloric lesions the indications for surgery are even more emphatic. The surgeon's responsibility in these cases is heavy. The differential diagnosis between simple ulcer and cancer is here always difficult, even at operation. The only positive information that the internist can give the surgeon is whether the lesion is an obstructing one or not. It is not safe to rely on the history, the X-ray or the laboratory in excluding cancer, for the reasons already stated.

It should make no difference in these cases if obstruction is present or not. Excision by means of some plastic operation is indicated.

Postpyloric Ulcer.—Passing from the stomach proper to the postpyloric region, the duodenum, we enter a field that is claimed by both medical men and surgeons. We have not the responsibility here of excluding primary cancer. The problem is principally one of obstruction. There are, to be sure, acute perforating postpyloric ulcers or those that persistently bleed; these the medical man should be glad to hand over to the surgeon, even when obstruction is not a factor. He is, however, loath to retire when not confronted by these emergencies or by obstruction, and rightly so, until he has proved by repeated trials that conservative measures are ineffectual. Those who are able to check up on the results of surgery and who are also familiar with the medical management of these cases are not willing to concede all that the surgeons claim for their treatment, and the surgeon is also justified in his criticism of the medical results in many cases. The reason for the discrepancy is largely due to a faulty understanding of the principles involved in the diagnosis in these cases and in the application of the treatment. It can be stated broadly that a postpyloric ulcer, if left to itself or badly managed medically, will sooner or later require surgical treatment, and it is possible that every postpyloric ulcer, except perhaps the acute perforating kind, at some time in its course could have been prevented from reaching the stage where surgery is indicated, by the proper medical treatment. The diagnostician, therefore, must not only be able to diagnose postpyloric ulcer; he should be able to say with confidence in a given case that it belongs to the surgeon or is one in which conservative measures should be tried.

In order to differentiate in these cases, a skillful use of the fluoroscope is essential. One can usually tell by this means if a postpyloric ulcer is badly indurated or not and can approximately estimate how much encroachment on the lumen has taken place. But it is rather the indirect evidence of beginning obstruction such as increased peristalsis, increased intragastric tension and the minor degrees of retention that are most valuable for this purpose. These minor degrees of obstruction do not, as a rule, cause vomiting; as a matter of fact, the patient usually complains of nothing but the characteristic hunger pains of the classical postpyloric ulcer syndrome.

Value of Gastric Analysis in Differential Diagnosis.—Gastric analysis is here of real value, particularly the Rehfuss method of fractional extractions, as we are thus able to judge of the motility accurately and to differentiate the retention due to spasm from that of organic obstruction. A stomach may successfully compensate for years through its muscular equipment a definite and gradually increasing obstruction. These are the cases from the very beginning of the obstruction that belong to the surgeon. But there is no logical reason for a gastro-enterostomy in any postpyloric ulcer until this stage has been reached, and it is rather surprising how large a percentage of cases, in spite of poor hygiene and faulty medical treatment, never reach this stage.

Medical Treatment of Postpyloric Ulcer.—Medical treatment should be attempted only in these cases of postpyloric ulcer in which it can be demonstrated that the gastric motility is normal. The failures in the medical management are due nearly always to the casual manner of the treatment. A Lenhartz or other intensive bed course is worse than useless, if not followed by a careful training of the patient, as it gives the patient a false sense of security. He should from the first be made to understand that he will always be subject to these attacks if he does not follow the "rules" and that, if he thus continues to provoke the attacks too often, the surgeons will surely "get him."

Ambulatory Treatment of Ulcer.—Before resorting to an intensive bed-treatment which is expensive and, to say the least, irksome, such a patient should be given a soft, non-stimulating, frequent-feeding diet; the calories increased somewhat above his needs; a generous and constant use of alkalis; petrolatum for constipation. Unless his occupation is one that interferes with this routine or is, for one reason or another, contra-indicated, he should be encouraged to continue at work. He should be given calisthenics and every attention paid to his general hygiene. It is hardly necessary to point out that these patients should be adjusted to their environment. While focal infection may play an important part in the etiology of ulcer, we must not lose sight of the fact that it is in part at least a neurotrophic manifestation and should be treated as such.

Gall-bladder Disease, Indications for Surgery.—The internist who feels that he can be as dogmatic in dealing with gall-bladder disease as he is in diseases of the stomach is indeed fortunate. It is not that all are not agreed that a definitely diseased gall-bladder is better out than in, or that an infected gall-bladder may not be a focus for serious trouble somewhere, particularly in the heart muscle.[2] Aside from the few cases where operation is contra-indicated for some good reason, the trouble is largely one of diagnosis.

It has been stated that about one in fifteen individuals harbor gallstones without ever suffering inconvenience. The occasional passage of such stones, while alarming and sometimes dangerous, is not always an indication for surgery, particularly if between such attacks the patients enjoy good health. As a matter of fact, these clear-cut cases of cholelithiasis present less of a problem than the masked cases; those in which the patient is evidently chronically ill and is subject to more or less constant nagging distress with perverted digestive functions and other constitutional manifestations. As time is not usually an element in these chronic gall-bladder cases, or those supposed to be, it has been found an excellent plan, before resorting to surgery, to regulate the patients' general hygiene and habits. By so doing, not a few of these cases will turn out to be nothing more than neuroses, of which mucous colitis makes up a large number. There is almost no disease of the abdomen which this troublesome secretory neurosis will not simulate.

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[2] The danger of secondary pancreatic disease should also be stressed.—Editor.

The tenderness in the upper right quadrant can easily be caused by a spasticity of the hepatic flexure of the colon. Acute angulation or other irregularity in this part of the colon may cause this tenderness and occasionally increased resistance as well. As a therapeutic test, therefore, the following procedure should be instituted in the doubtful cases. The diet should be made up largely of bulky foods, but it should be low in cholesterol-forming elements. The obese patient should be reduced, if possible, through a manipulation of the diet, and by exercise, and agar-agar used for the bowels; the Carlsbad treatment is also occasionally of value.

By treating these patients conservatively for a time, not a few of them can be relieved; not because such treatment could have much effect on a diseased gall-bladder, but because the constipation, colitis or whatever had really caused the symptoms has received appropriate attention. When this plan has been persisted in sufficiently long to demonstrate that we are really dealing with a diseased gall-bladder and not a neurosis, we should then call in the surgeon, and, should he operate, the patient will be in better condition to undergo the operation because of this preparation.

Chronic Appendicitis.—The surgeon who can in these days make a diagnosis and operate in a case for chronic appendicitis with no previous history of acute attacks, basing his diagnosis on irregular indigestion and tenderness over McBurney's point, or on the radiographic findings of an appendix that retains barium unduly long, is indeed brave. But one, if he employs an efficient follow-up system, is bound sooner or later to acknowledge (to himself at least) that, in a fairly large percentage of these cases, he has either been in error in diagnosis or that surgery is not the last word in the treatment of these indefinite cases.

Dr. Charles L. Gibson some time ago realized these possibilities. After a research in his follow-up clinic he arrived at some interesting conclusions:

The series included 555 cases in which he had operated for chronic appendicitis and the patients had later been investigated by his follow-up clinic:

"In 259 results excellent.
"In 65 results satisfactory.
"In 102 results unsatisfactory, unimproved.
"In 126 no reports received; 3 had died."

After classifying the various cases according to age, sex, nationality, etc., he concluded with the following:

> "A complete, detailed history and thorough physical examination, with all the refinements of diagnosis, are essential. Extreme caution should be used in undertaking such operations on women as compared to men, and extreme caution when dealing with the more mature patients, particularly women in this class, as other lesions may coëxist. Avoid neurasthenics of any age or sex. Exercise particular restraint when there is no clear-cut and reliable history of well-defined attacks of localized pain accompanied by nausea and vomiting."

He states that nearly all of the patients who had been operated on for acute appendicitis had remained symptomless and well.

There is a syndrome that has in a large percentage of cases proved valuable in diagnosis:

A tender McBurney's point with the pain on pressure reflected to the midepigastrium.

A high acid, continuous secretion type of gastric secretion; in other words, a high acid curve maintained beyond the normal (according to the Rehfuss fractional method).

A persistent spasm of the antrum observed fluoroscopically.

Constipation.

There are many cases of indefinite indigestion that are thought to be due to chronic inflammatory changes in the appendix in which relief can be obtained by a regulation of the patient's hygiene. Here a bulky laxative nutritious diet will be found valuable, supplemented by the use of agar-agar, but no other laxatives; much drinking of water both with and between meals; the support of the abdomen by means of corsets and bandages; carefully directed physical training. Here, as in disease of the gall-bladder, the indications for surgery depend on correct diagnosis. It is quite obvious that where there are actual inflammatory changes in an appendix it should be removed, but an appendectomy performed for the relief of irregular indigestion where the history and findings do not definitely point to such changes is bad practice.

Surgery in Gastric Carcinoma.—Except as a palliative measure, surgery is contra-indicated in gastric carcinoma when it can be demonstrated that the lesion is so extensive that there is little doubt of its extension beyond the limits of the stomach. Even when such a growth is small and favorably placed for excision, if the mobility of the organ is impaired to any extent, one is not justified in ordering a radical operation. Surgery is obviously contra-indicated in cases in which metastases can be demonstrated or abdominal ascites proved. This narrows the operable cases considerably. These, therefore, include only those in which the lesion can be demonstrated to be small and favorably placed for excision, or to those cases in which the diagnosis has not been established beyond a reasonable doubt. Where a growth obstructs and a radical operation is contraindicated, a palliative gastro-enterostomy will not infrequently prolong life and relieve pain, vomiting and other distressing features in these tragedies.

PRINCIPLES OF DIET IN GASTRO-INTESTINAL DISEASES

It would be quite impossible adequately to cover in a part of one chapter the subject of diet in digestive diseases, but it is thought so vital a part of gastro-intestinal practice that some consideration of the vaguely understood principles of diet cannot be passed by.

In reviewing the literature only casually, one can plainly see the influence of fads and pseudoscience, largely imported from Europe, in the diet lists put forth. We may not have anything more scientific to offer, but we should weed out these encumbrances and unnecessary restrictions and proceed rationally according to our lights.

The chemical action of foods on the digestive apparatus is to be considered in arranging a diet in the treatment of a digestive disease, but quite as important is the physical character of the foods and the manner of their serving. Very little can be hoped for in effecting any change in a lesion in the digestive canal through a manipulation of the diet alone. It is true that some change in the intestinal flora may be accomplished by following the Torrey alternating diet, but apart from this the problem is largely in arranging a diet for the particular disease that will do the least harm and cause a minimum of embarrassment to the processes of repair that are made possible by rest, medication or whatever form of treatment has been instituted.

High Acid in Ulcer.—In ulcer of the stomach or duodenum it is thought that the high acid, which is a distinguishing feature of this disease, is not a cause of the lesion but the result of it. It probably comes about directly through the irritating effect of the lesion, through spasm and hyperperistalsis incident to the lesions, also through the deficient motility of partial or complete obstruction.

Causes of Pain in Ulcer.—It can be demonstrated that the pain of ulcer is not caused by the high acid; it seems to be due to increase in tension in the zone of the ulcer; or when that part of the stomach is most concerned in peristaltic activity. This can be demonstrated by the administration of a carbohydrate and barium meal, observed fluoroscopically at frequent intervals coincident with a fractional extraction and analysis of the contents. The diet in these cases should, therefore, not be planned entirely with a view to decreasing or combining this acid. It should be one that will cause the least stimulating effect on the motor mechanism, and it should be of such consistence that it will pass out of the stomach and duodenum with a minimum of effort of these parts.

Effect of Solid Foods on Pylorus.—It has been found that food in a solid state, pieces of meat, uncooked vegetables and fruits, when forced against the pylorus by the contractions of the antrum, prevent a relaxing of the valve. The antrum is also stimulated to increased activity and the peristalsis of the entire stomach is increased. Food in a fluid or semifluid state passes out rapidly without exciting this motor activity to any marked degree.

Emptying Time; Carbohydrates, Proteins, Fats.—The carbohydrates normally remain a relatively short time in the stomach. The proteid elements are retained twice as long; combined and free fat remains the longest. Fat combined with other foods will cause delay in proportion to the amount of fat present. The difference in the emptying time between these elements when all are of a soft consistence does not compare with the delay that is caused by any one of them when in a solid state.

In studying various barium meals fluoroscopically, the writer has found that in ulcer the pain is not coincident with the regular peristalsis that fluid and semifluid foods excite, but that it is usually coincident with the violent contraction of the antrum toward the end of gastric digestion, after all the soft foods or fluids have been decanted off, leaving the solid residue to be grasped by the antrum and forcefully expelled through a reluctant pyloric valve. It is this severe muscular effort and not high acid that is responsible for pain, and as pain is the most reliable measure we have of ulcer activity, it is reasonable to believe that this muscular activity is responsible for much of the delay in the healing of gastric and duodenal ulcers.

Diet in Ulcer.—Milk and eggs are ideal foods in treating ulcer. They are excellent acid binders and they excite peristalsis only moderately. Their conversion into chyme is so gradual and even that their expulsion from the stomach is accomplished with relatively little effort. The well-cooked carbohydrates are also valuable, but their bulk is somewhat of a handicap. Bulky meals, even when of soft consistence, excite peristalsis in proportion to the bulk.

Fats Valuable in Ulcer.—While the fats may cause delay in emptying, their high caloric value renders them invaluable in an ulcer diet; they seem to quiet excessive peristalsis and inhibit to some extent the production of acid. The writer has found olive oil a most useful food adjuvant in these cases.

Lenhartz and Sippy Diets.—The Lenhartz and Sippy diet systems differ somewhat in application, but they adhere in a general way to these well-known principles. The Lenhartz diet is rather more intricate and, therefore, not so easy to carry out except in a hospital. But in a case where the patient has become debilitated through bleeding or undernourishment, it is probably the safer procedure.

In reviewing his experience with these and other systems of diet, the writer is forced to conclude that there is very little difference in the results; that the rest in bed which is common to them all is the most potent element in the relief; and he is not too sure that this does not also apply somewhat to the surgical treatment of ulcer where excision is not practiced.

In the past few years the writer has in his private practice refrained from using any of these bed courses, except in the extremely bad cases. The patients have been encouraged to remain at work; they have been given a high-caloric, frequent-feeding, soft diet; the high acid has been constantly neutralized, their hygiene supervised and improved through exercises and a regulation of the habits. The ultimate results of this method of treatment have been satisfactory; quite as good and lasting as from any of the more drastic methods; better than when the bed treatments have not been followed by prolonged dieting and care.

It should not be necessary to caution against the use of condiments and alcohol in these cases and against foods that stimulate because of an excess of aromatic principles, such as grapefruit, raw strawberries, onions, rhubarb and cranberries. The uncooked fruits and vegetables generally are to be avoided—bananas and alligator pears excepted. These patients cannot get on entirely without some meat. At the beginning of the treatment, in addition to the milk, cream and eggs, the tender kinds of meats should be allowed. White meat of chicken and bird game, calves' brains, sweetbreads, raw oysters and fresh fish are of those least harmful. Even these should be minced at first. Rare tender roast beef and lamb can usually be added after a month or two of treatment. But pot roast, pork, duck, salted or preserved meats and smoked or salted fish, liver and kidneys should be allowed only after several years have passed without acute exacerbations. The patients should be impressed with the importance of taking only small meals at frequent intervals.

The writer's diet for ambulatory treatment of ulcer:

Morning.—A teaspoonful of olive oil fifteen minutes before eating.
One or two tablespoonfuls of stewed fruit, a baked or steamed apple without skin or core, or a sliced scraped banana, all served with cream and a little sugar.
A cup of coffee, cocoa, hot malted milk or a glass of milk.
A small saucer of any thoroughly cooked breakfast cereal with milk or cream and sugar.
One soft-boiled egg.
A piece of toast with butter.

Two hours after breakfast a glass of milk, buttermilk or malted milk.

Noon.—A teaspoonful of olive oil fifteen minutes before eating.

Minced chicken, squab, sardines, salmon, or any fresh minced fish (these soft articles may be used in sandwich form), or a portion of creamed sweetbreads, broiled brains, small raw oysters, creamed chipped smoked beef, or eggs, poached, scrambled, creamed or omeletted.
One slice of bread and butter (if sandwich is not taken).
A cream puff, éclair, ice cream, or any soft sweet pudding.

Two hours after luncheon a glass of milk, buttermilk, malted milk, hot chocolate, or a dish of vanilla or chocolate ice cream.

Evening.—A teaspoonful of olive oil fifteen minutes before eating.

A cream soup, thoroughly strained, made of corn, cauliflower, celery, oyster plant, lettuce, spinach, potatoes or mushrooms.
Two soft-boiled, poached or omeletted eggs.
A tablespoonful of mashed or baked potato, spaghetti, noodles, or rice.
A small portion of any fresh green vegetable puréed.
One slice of white bread with butter.
Stewed fruit with cream, gelatin with cream, cream puff, éclair, vanilla or chocolate ice cream, or any soft sweet pudding.

At bedtime a glass of milk, buttermilk or a cup of cocoa.

Do not eat or drink anything that is not mentioned on this list, except water in small quantities between meals.

Use no seasoning except a sprinkle of salt.

Use no rich sauces or gravies and no soups made with meat or meat stock.

All food must be soft; the vegetables thoroughly mashed and when possible strained.

Eat slowly. Chew all food thoroughly. Hold each mouthful long enough in the mouth for the saliva to become thoroughly mixed with the food before swallowing. Even the liquids should be held in the mouth for a short time before they are swallowed.

Smoke only after eating, if at all.

Do not drink alcohol of any kind.

The teeth should be put in perfect condition, all cavities filled and artificial teeth placed where the natural ones are missing. When possible rest for fifteen minutes to one-half hour after eating.

Diet in Gastritis.—Primary gastritis is a comparatively rare disease, but secondary inflammatory changes in the stomach are fairly common. The diet suitable for these cases (both primary and secondary gastritides) depends somewhat on the secretory status of the organ. In an irritable stomach where there is an excess of acid (this is usually called acid gastritis) the frequent-feeding, soft diet suggested for ulcer is indicated. The carbohydrates are not well tolerated by these patients, as the starch digestion within the stomach is embarrassed somewhat by the excess of acid. Tender meats, eggs, milk, cream and butter and the puréed green vegetables and fruits are here indicated. When the acid is low or absent, more reliance should be placed on dairy products, cereals, puréed vegetables and fruits. The absence of acid makes digestion of meat difficult, as the white fibrous stroma between the meat cells is normally digested in the stomach as is also the fat envelope. In the severe cases, therefore, only scraped beef (not chopped) should be used at first and meat fat avoided. Butter fat, being free, is fairly well tolerated.

Diet in Gall-bladder Disease.—The indigestion which is secondary to disease of the gall-bladder comes about in two ways: reflexly, and as a result of impaired fat digestion. Most of the symptoms in the masked cases are the expressions of spasm and hyperperistalsis which are reflexly excited in the stomach. The irregular onset of these symptoms in relation to the taking of food is thus explained, as is also the irregularity in the intolerance for various articles of diet: one day, meat or some other article may disagree, to be taken the following day without causing symptoms. The intolerance for fat in any form is a fairly constant complaint of these patients. It is due to a different cause: to the inability of the gall-bladder to empty properly, thus depriving the fat of the necessary preparation for final digestion.

In making up a diet for these patients these points should be kept in mind. Not too much attention should be paid to the supposed intolerance for any of the usual foods, except those that contain an excess of fat. Many of these chronic sufferers are constipated, due largely to a reflex spasticity of the colon, so that, when possible, bulky, laxative foods should be given preference. Those vegetables that contain an excess of the cholesterol-forming elements, such as peas and beans, are not to be included. Hypercholesterolemia is undoubtedly of considerable etiological importance in gall-stone formation.

Diet in Chronic Appendicitis.—The indigestion of chronic appendicitis, like that of chronic gall-bladder disease, is largely dependent on spasm and other erratic behavior of the motor mechanism of the stomach reflexly excited. It is therefore not necessary to pay too much attention to the supposed food idiosyncrasies of these patients. But one must give some thought to arranging a diet that will be as little irritating to the colon as possible and one that will tend to promote a normal bowel function. As laxative medication is usually contra-indicated in these cases, a bulky laxative diet is essential; one that will insure sufficient moisture in the contents of the colon, but that will not cause undue fluidity of the feces. The stewed fruits, fruit juices, green vegetables, starches and fats are all indicated, with a minimum of meat. Agar-agar is a valuable adjuvant in these cases, but uncooked bran is too irritating. These patients should be encouraged to drink much water, both with and between meals.

Diet in Constipation and Colitis.—It is now many years since the von Noorden diet system for treating chronic constipation and chronic colitis was inaugurated. In a modified form it is still relied upon. The principle is in the supplying of bulk to the colonic contents, in this way encouraging a return to a normal tone of the colon through an exercise of its musculature. Not only is this necessary in hypotonic and atonic constipation and colitis; it is found quite as essential in the spastic states. But in the latter conditions the rougher elements should be used with care. It requires no little faith and conviction to persevere with a bulky laxative diet in a case where constipation alternates with attacks of diarrhea. But this has been found the best plan in the long run. Agar-agar can hardly be dispensed with in either form of constipation. Much water should be taken both with and between meals.

For the treatment of atonic constipation and chronic colitis the writer would suggest the following schedule and diet:

On arising.—Two glasses of cold water.
Exercise for ten minutes (see illustrations).
A cold bath or if this is not well tolerated take a warm bath and then a cold shower or slap the abdomen with a towel wet with cold water.

Breakfast.—A cup of coffee, with cream and sugar, or a glass of hot malted milk.
A dish of stewed fruit of any kind, baked apple with cream, orange, grapefruit, ripe cut-up peaches, ripe pears, mellow sweet apples, occasionally cantaloupe, berries, grapes and cherries in season.
A large dish of corn-meal mush, oatmeal or Pettijohn's (thoroughly cooked), served with milk or cream, or butter and sugar.
Bran, corn or whole-wheat bread with butter, and with marmalade if desired.
No eggs, but occasionally some crisp bacon.

Luncheon.—A glass of acidophilus cultured milk or plain buttermilk.
A soup of asparagus, celery, mushrooms, lettuce, corn, peas, beans, tomatoes, or any other vegetable that can be puréed. (No soups made with meat or meat stock.)
Any fruit, vegetable or mixed salad, or any combination of cooked green vegetables.
Bread as for breakfast.
Stewed fruits, baked apple, fruit puddings with cream.
Fresh gingerbread, fig-newtons, or molasses cookies.

The above may be taken at night as well.

Dinner.—Soup as for luncheon.
A small portion of beef, lamb, veal, chicken, fish, steak or chops (no pork, duck, goose, or any salted or preserved meats or smoked or salted fish).

Two green vegetables such as corn, peas, string beans, asparagus, Brussel's sprouts, cabbage, onions, parsnips, beets and beet tops, spinach, kale, lima beans, squash, cauliflower, tomatoes, stewed or raw, artichokes, egg plant, oyster plant, turnips or carrots.
One starchy vegetable such as rice, macaroni, spaghetti, noodles, white or sweet potatoes.
A lettuce or vegetable salad, French dressing.
Bread as for breakfast.
Stewed fruits, baked apple, occasionally cantaloupe, fruit puddings, with cream, gelatin with cream and fruit, rice pudding with fruit and cream; occasionally plain cake or cookies.
Demi-tasse if desired.

The above may be taken at noon if desired.

One glass of water may be taken with each meal and one glass between each meal. Take a different kind of fruit with each meal and from day to day. The vegetables should be thoroughly cooked—puréed when possible. The meats should be roasted, broiled or boiled.

Spastic Constipation.—Where there is any considerable degree of colonic spasticity present, the uncooked fruits and raw vegetables are omitted from the list and the meats excluded entirely during acute exacerbations.

Alternating Diet for Protein Putrefaction.—When protein putrefaction can be demonstrated as a result or an accompaniment of constipation or colitis, by the use of the alternating diet suggested by Torrey, a change in the intestinal flora is accomplished. This will not infrequently overcome for a time the putrefactive process. E. J. Best suggests a practical application of this diet:

Alternating Diet.
First Four Days. Diet No. 1:
DO NOT EAT: Meat—which includes all flesh in any form, as beef, chicken, fish, oysters, ham, bacon, or any soup or gravy made from meat stock.

EAT: Starchy foods—bread, potatoes, rice, macaroni, sago, crackers, cornstarch, pastry, mush, cereals, milk, ice cream, sugar.
Fats—butter, cream, lard.
Green vegetables of all varieties.
Proteins—eggs, three to four daily (cooked), cheese (three to four cubic inches).
Fruit—as desired.

Important: Take at least one tablespoonful of sugar of milk with each meal, using it as you would cane sugar.

Three Days (following above four days). Diet No. 2:

EAT: All kinds of meat, in any form, at least twice a day.
Only one piece of bread with each meal.
Only one *small* potato, once a day.
Only one tablespoonful of rice or macaroni, at meal when no potato is eaten.
Eat green vegetables without flour sauces.
Desserts of fruit and gelatin, but no pastry.
Eat very little sugar.
Use no milk sugar.
Milk taken in small quantities only, if at all.

On completion of Diet No. 2 return to Diet No. 1.

Note.—It is best to eat three or four times a day. Tea and coffee used according to one's habit.

This alternating diet should be adhered to for two or three weeks and then the patient allowed to return to his regular diet for a week, followed by a week of the alternating diet. Then two weeks of the regular diet to one week of the alternating. It would be well for the patient occasionally to return to this system even after he appears to be cured.

GAVAGE

There are diseases and emergencies in which feeding by tube becomes necessary. In pediatrics it is frequently resorted to, but in adult practice it is not so often used, being reserved for emergencies when patients are unconscious or for one reason or another are unable to swallow, and in the treatment of the insane.

By Nasal Tube.—When the patient is unconscious or insane, a nasal feeding tube is easier to pass and less apt to enter the trachea than the ordinary stomach tube. For this purpose a tube of No. 20 French size is employed. The patient, properly protected and with arms restrained either by a restraining jacket or sheet, is placed in the supine position. The tube, well lubricated with olive oil or some other simple lubricant, is passed slowly into the nostril. As it passes in the patient's breathing should be watched for evidence of embarrassment such as coughing or choking. The fluid meal should not be introduced until it is certain that the end of the tube has entered the stomach. Frequently when a tube does enter the larynx it may give no apparent discomfort to the patient, but one can usually hear the breath inhaled and exhaled through the tube. It should under these circumstances be withdrawn at once and another attempt made to pass by the larynx. Forty to 45 cm. is the approximate distance from the nostril to the stomach. The technic for passing the ordinary stomach tube is the same as in lavage, described under that heading.

Where haste is not imperative, a preliminary lavage is beneficial. In the insane, particularly the depressives, gastric motility is, as a rule, retarded and this preliminary lavage, by cleaning out stagnant and fermented food and accumulations of mucus, promotes a better tone and secretory function.

Any food that is sufficiently fluid to pass through such a tube may be used. As a rule it is better not to completely fill the stomach. From 100 to 300 c.c. should be enough. The most concentrated foods should be given preference, as the procedure is disagreeable and a severe strain on the patient, and should be repeated only as often as absolutely necessary. Milk and cream, beaten up eggs, cocoa, cream soups and gruels are the common articles used. Lactose adds considerable caloric value to such meals, also whisky and sherry when not contra-indicated.

DUODENAL FEEDING

Einhorn and others have for many years used the duodenal feeding tube in treating gastric and duodenal ulcer and gastric atony. Except in ulcer high up in the body of the stomach the writer has not had any personal experience with this method. Notwithstanding the many favorable reports on this procedure, he believes that the principle is wrong, that whatever is gained in resting the secretory apparatus of the stomach is lost in the spasm and irritation the tube must constantly excite. The loss of gastric digestion and its effect on nutrition must be reckoned. The psychic reaction of many patients to this form of treatment is not good.

The passage of the duodenal tube for purposes of alimentation is accomplished as described under Duodenal Lavage. Einhorn's procedure for the feedings as described by him is as follows:

"The food is usually given every two hours, eight feedings a day. The standard food is milk (7 to 8 ounces), one raw egg, and a tablespoonful or two of lactose. The lactose sometimes creates diarrhea and should then be omitted. In some cases, where it is essential to see that there is no loss of flesh, butter (1 to 2 drams) may be added in every alternate or in each feeding. It is then necessary to add a teaspoonful of fine flour to each feeding, in order to bind the butter and effect a thorough mixture. Only a few patients cannot stand the milk, the latter creating such a disturbance that it must be eliminated. Such patients tell you that they never could take milk anyway. Here, instead of milk, water with barley or pea flour or vegetable milk may be substituted. Whatever is fed to the patient must be of blood temperature—neither cold nor hot—and it must be given slowly.

"With regard to the method of feeding again: The temperature must be just right. The food introduced must be free from thick particles. All the food should be strained because in passing through the long, fine tube the latter would easily become clogged, if this precaution were not taken. The smaller the tube, the pleasanter for the patient; but, on the other hand, the more difficult the handling of it. After each feeding, before closing the stopcock, a little water and then some air should be injected in order to keep the tube always empty. If one is not careful to clean out the tube with water and air, the end becomes clogged in a day or two, and the tube has to be taken out and replaced, with a great deal of inconvenience to the patient, as well as to the doctor and nurse, and that tube is often spoiled. Where patients are under strict supervision, nothing of that kind happens. It is simply faulty technic when it occurs.

"The tube is left in permanently during the course of this treatment, and the patient's mouth should frequently be washed out with some good mouth wash. If these patients do not eat anything, there is nothing to cleanse off the surface of the tongue, and it is very essential that that should be kept clean.

"Outside of the feeding, the patient is given a pint or a quart of saline by the duodenal tube. The saline may be given either with the syringe or by connecting an irrigator to the tube. The main point is to let the fluid run in slowly and at blood temperature. If the patient does not like that, it may be given into the rectum by the Murphy drip method, for the bowels absorb saline very well. The food is the vital thing. By this method we accomplish perfect nutrition and everything is utilized.

"It is self-understood that many other nutritive materials may be given through the tube, provided they do not clog up the pipe. Thus all kinds of soups (beef, vegetable or cream), beef juices or extracts, likewise fruit and vegetable juices, thin gruels, emulsions of nuts and sweet almonds, condensed or dried milk (dissolved in water), fine meat powder or cereal flours well diluted may be employed. One precaution should be repeated, namely, that everything given through the tube must be strained."

CORRECTIVE EXERCISES IN GASTRO-INTESTINAL DISEASES

The indications for a course of corrective exercises should be as definite as the indications for any form of treatment. When given in a gymnasium it is an expensive procedure, time-consuming and irksome to most people. In not a few cases it is contra-indicated. There is a prevalent belief entertained by laymen as well as many physicians that in physical training lies the key to health. It is very true that most people in ordinary life exercise too little and that many ills, in part at least, are caused by sedentary habits. But that defects which are the result of lifelong habits or inherited structural abnormalities can usually be rectified by means of corrective calisthenics is not entirely true. As a matter of fact, there is a very definite limit to what can be accomplished by this form of treatment, particularly for patients no longer young. Perhaps a great deal of the benefit derived from physical training comes through the mental discipline involved. The patient who can be induced to arise fifteen minutes earlier each day in order to indulge in a set of exercises followed by a shower bath is very apt to go through the day carrying with him a sense of fitness that is not conducive to slothful habits of mind and body. Many patients after a course of training, in order to escape the grind of it all, but realizing through the experience the benefits to be derived, substitute the outdoor sports and occupations, and this is indeed a happy result.

Indications for Corrective Exercises.—The indications for corrective exercises in gastro-intestinal diseases are as follows: General muscular asthenia in which there is evidence of a lowering of the intra-abdominal tension, with a resulting visceroptosis and atonia of the stomach or intestines; constipation of the atonic variety and spastic constipation that may be secondary to ptosis or other structural defects. In simple obstipation there is less indication for this training, except as a means for strengthening the muscles which indirectly help in the final act of defecation. In many cases that present irregular gastro-intestinal symptoms that are supposed to be reflexes from a chronic appendicitis, but in which a history of definite attacks of acute appendicitis is lacking, such treatment, combined with a regulation of the diet, will not infrequently obviate surgery. In chronic appendicitis where there is no doubt of the diagnosis, but where operation is refused, deferred, or contra-indicated, there can be no objection to general tonic calisthenics, but those special abdominal exercises should be avoided which might cause trouble in the lower right quadrant because of undue pressure or trauma.

These same limitations apply also to gall-bladder disease. When by a process of elimination a gall-bladder is *suspected* of being the cause of an irregular type of indigestion, but where no direct evidence of gall-bladder involvement is obtainable, and in the absence of a history of acute attacks, improvement in the general condition will frequently be made possible through physical training and the gall-bladder will be proved innocent. One would hardly care to take the responsibility of ordering strenuous abdominal calisthenics in a case where a gall-bladder is known to be diseased, but pending operation such patients should be encouraged to do setting-up exercises, ordinary housework or the lighter outdoor sports. Hypercholesterolemia is less apt to obtain when oxidation is promoted as it is by exercise, and this is desirable for those of this habit.

Pelvic disease is usually a contra-indication. In any of the general diseases in which loss of weight is a feature, or where there are any inflammatory lesions present, exercises should be ordered with great caution.

Ulcer of the stomach is a surgical problem because of the danger of perforation or the possibility that such an ulcer may be carcinomatous. Special efforts at abdominal exercise are here obviously contra-indicated. But even in these cases, pending operation, the general condition should be kept in tone and the circulation mildly stimulated by an adequate use of the general muscular system, through the milder exercises—not, however, during or immediately following acute exacerbations. This is also true of postpyloric ulcer, but in these cases surgery is not always indicated, as cancer is not here a possibility. The danger of perforation, however, is quite as great and one should be exceedingly careful in prescribing exercises in these cases, notwithstanding the great benefit that such hygienic measures offer.

For the neurasthenic individual whose posture or carriage is bad, or who suffers from any degree of myasthenia or who is markedly enteroptic, physical training is of great use. But the hypochondriac who has not these physical defects to blame is in most cases only made worse by such attention to his body. It may for a time divert his attention from medication, electricity, and other such forms of treatment, but it as a rule only serves to fix his attention more intently on his imaginary disease. The argument that "physical training can at least do no harm in such cases" is, therefore, not true. It is far better for these patients to be put at some interesting productive work.

There is another class of patients who suffer from gastro-intestinal disturbances, for whom physical culture can promise little, and yet whose physical make-up would seem to indicate its need: the asthenic, anemic, overworked young or middle-aged woman, occasionally of the professional class, but more frequently found struggling for an existence as a shop-girl, seamstress, or even a factory worker. In these cases some endocrine disturbance or deficiency is usually apparent but difficult of classification.

Here rest, hyperalimentation and conservation measures should precede any attempt at physical training of even the mildest nature.

Posture.—The erect, easy posture of the strong healthy person is in marked contrast to that usually assumed by the one whose morale is lowered through functional or organic disease. One of the first requisites to health is the individual's pride and confidence in his body as a machine, and this is usually reflected in his posture. This need not approach that extreme attitude of the pugilist, but it should at least not suggest fear. Important as this is to the individual's moral welfare, it is infinitely more so in the interests of body function. Lungs that are limited in expansion by drooping shoulders cannot be thoroughly efficient. The laws of gravity and of the inclined plane are operative within the abdomen as elsewhere, and, where the operation of these laws is embarrassed through faulty lines of force, impaired function can only result.

The correcting of postural defects presents many difficulties. Calling the attention of the intelligent patient to his abnormal body contour will occasionally help as a start, but the actual training is long and tedious. It should center first on the spine, and those exercises which tend to strengthen the trunk muscles are to be pushed, attention given to the proper training of the diaphragm and the muscles of the chest, particularly those that act in lifting the ribs. The parallel bars, swinging rings, rowing machine and pulley and weights are the apparatus best suited to this purpose. But when an instructor is available, setting-up calisthenics, Indian club and wand drills, fencing and boxing are to be preferred to the apparatus work.

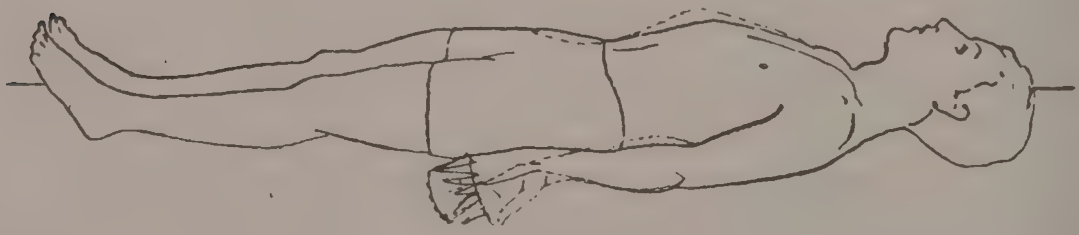
Carriage.—The teaching of graceful, easy carriage is even more difficult than the correcting of postural defects. Dancing should help, but it does not seem to. Swimming does, however, possibly because of the coordination necessary between the breathing apparatus and rhythmical use of the legs and arms. When patients can be impressed with the importance of perfect coördination in walking and dancing, as they are early in learning to swim, it is not so difficult to modify their bad habits of carriage. Too little attention is paid to the swing of shoulders and arms and to the type and rate of breathing suitable for the gait or stride of the individual.

The average person in his ordinary routine of life, even though his occupation be a more or less sedentary one, makes considerable use of the muscles of his arms, shoulders and legs. The act of sitting erect all day makes many demands upon the muscles of the trunk. The abdominal muscles, however, are usually neglected, as well as those of respiration both true and auxiliary. It would seem, therefore, that if any time is to be spent in special body training, these parts should receive first consideration, particularly in gastro-intestinal practice. It will be seen that the exercises illustrated (Fig. 1) bear directly on the abdominal muscles and those of the respiratory apparatus. The strengthening of the abdominal muscles through exercise is desirable because of the resulting increase in intra-abdominal tension which is so often reduced because of lax abdominal walls. This is important, but quite as essential to well-being is a normal tone for the hollow organs within the abdomen. While we cannot hope directly to reach the muscular coats of these organs through exercise, the deep massage that they receive in these special abdominal calisthenics does seem to help considerably. This automassage is very much more efficient in accomplishing this result than is the pounding and kneading administered by a masseur. It is reasonable to expect that the circulation of the blood in the abdomen is thereby stimulated as well as the flow of lymph and other juices promoted.

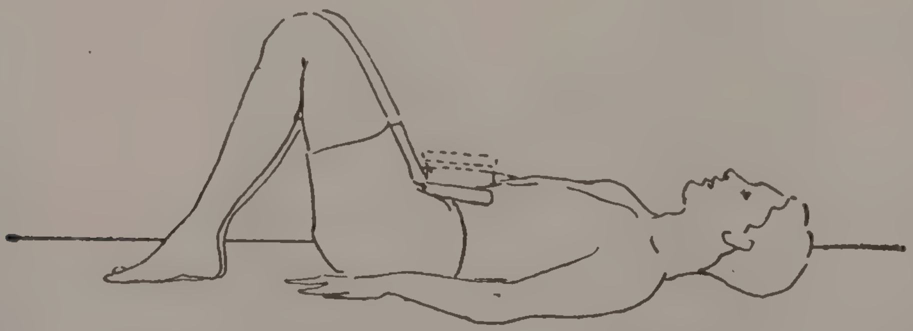
In prescribing abdominal exercise it is difficult to estimate correctly a patient's tolerance before he is tried out. When the treatment can be given in a gymnasium under a competent director this is easily arranged. For home treatment without such supervision, a chart similar to that which is here illustrated (Fig. 1) can be utilized. Starting with several movements, the patient should gradually increase the number of exercises each day until a tolerance is established. The early morning on arising is by far the best time of day for this performance; or when this is not practical it can be done an hour before luncheon or dinner—never soon after eating and never just before retiring. It is always well to follow the exercises by a shower—cold, if a pleasant reaction is obtained. But this should not be insisted on as it offers no great advantage. A brisk rub-down with a coarse towel will give quite as much reaction. When time will permit, a few minutes' rest in the supine position with a complete relaxing of all muscles should follow the exercises. Patients should be impressed with the importance of learning how to relax when resting at any time. There is nothing quite so important to proper muscular function as physical poise and graceful easy carriage through this art of complete body relaxing.

FIG. 1.—ABDOMINAL EXERCISES—MCGOVERN METHOD. (Courtesy of McGovern's Gymnasium.)

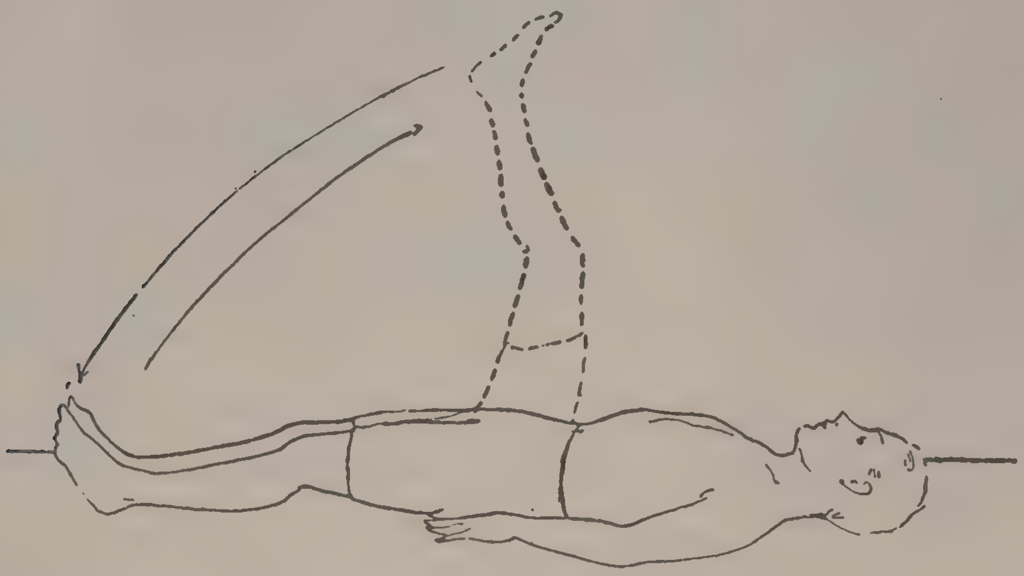
SET NO. 1



Exercise No. 1—Breathing: Lie flat on your back, hands at your sides, palms down. Take a deep slow inhalation, raising chest high, bringing your abdomen in and turning palms up, with shoulders to the floor—hold breath for five seconds. Exhale, returning to a relaxed position, turning palms downward.

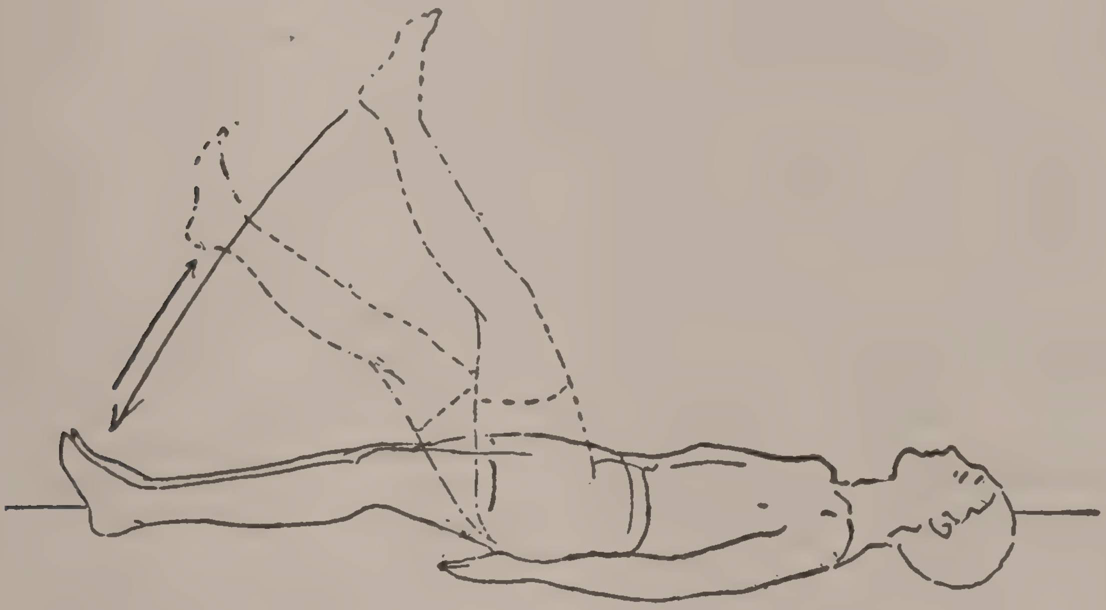


Exercise No. 2—Lie flat on your back. Draw knees up with both feet on floor. Place a weight (a heavy book will do) on abdomen. Raise the weight up by contracting the stomach muscles and lower it by relaxing these muscles.

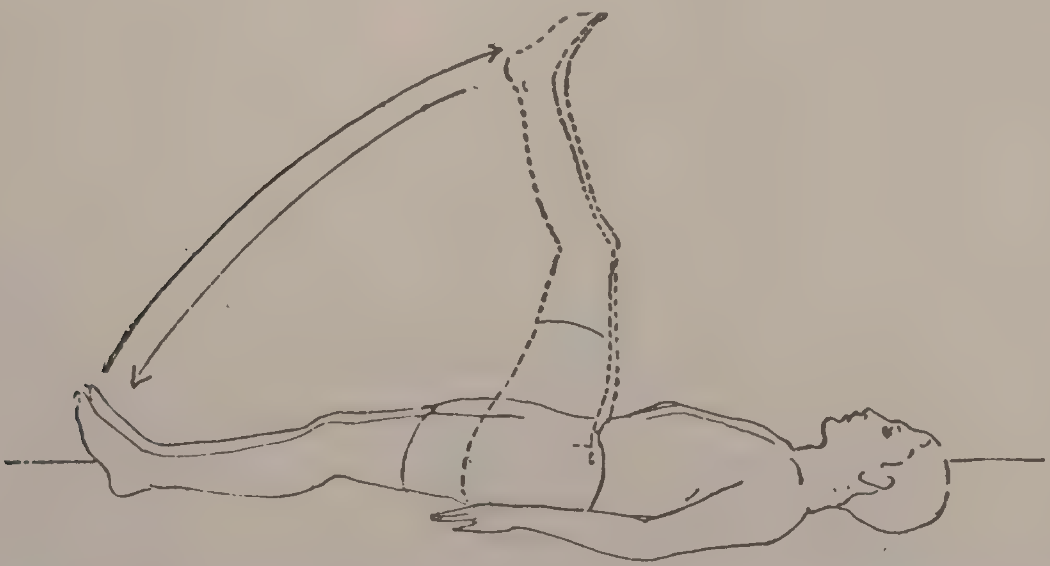


Exercise No. 3—From flat position, place palms down, legs out straight. Raise right leg up as far as possible, keeping your leg straight, toes pointed.

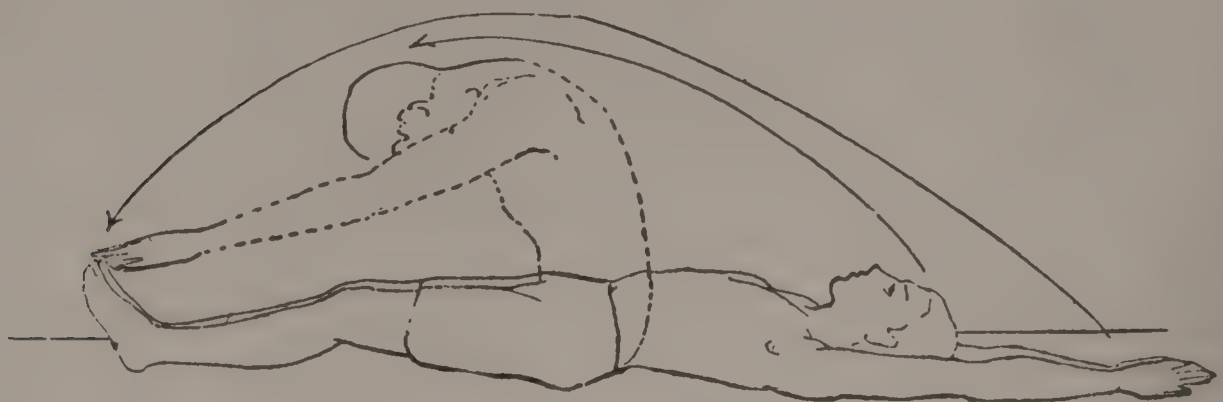
Exercise No. 4—From flat position, place palms down, legs out straight as in No. 3. Raise left leg up as far as possible, keeping your leg straight, toes pointed.



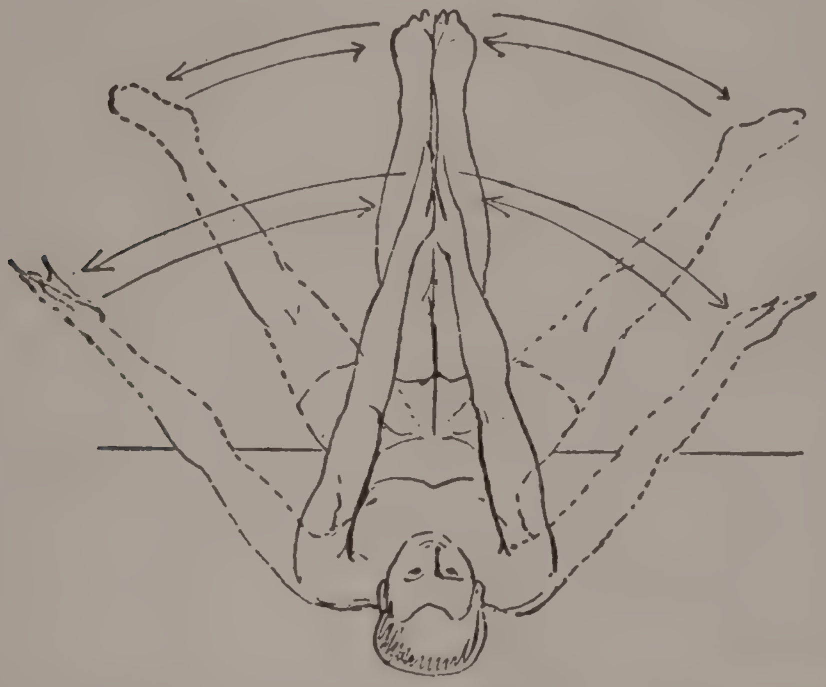
Exercise No. 5—From flat position, raise legs from floor. Swing left and right leg alternately. Legs stiff, toes pointed and do not touch the floor until exercise is completed.



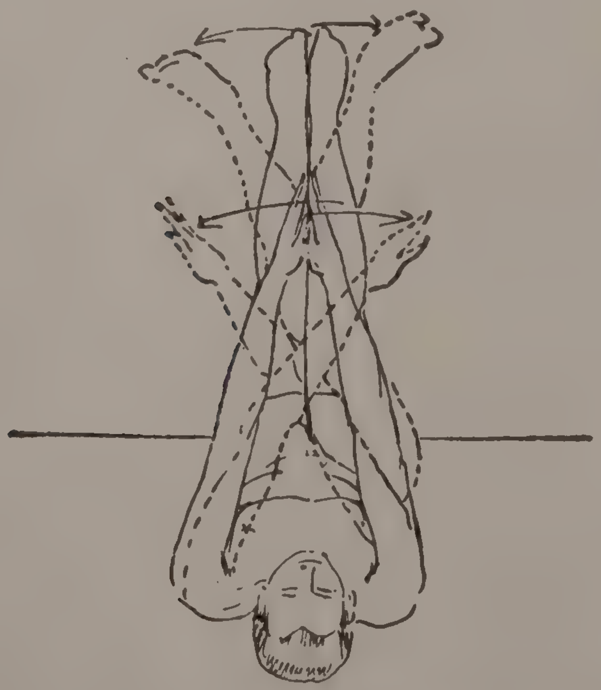
Exercise No. 6—From flat position, raise both legs together from floor, and bring down together, legs straight.



Exercise No. 7—From flat position, hands straight behind head, raise body to sitting position (without bending knees) trying to touch toes with finger tips.



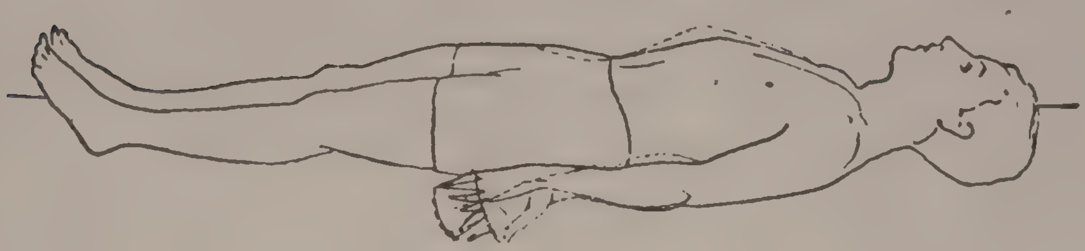
Exercise No. 8—From flat position, raise hands up straight, legs up straight, toes pointed, knees stiff, spread hands and feet and bring together again.

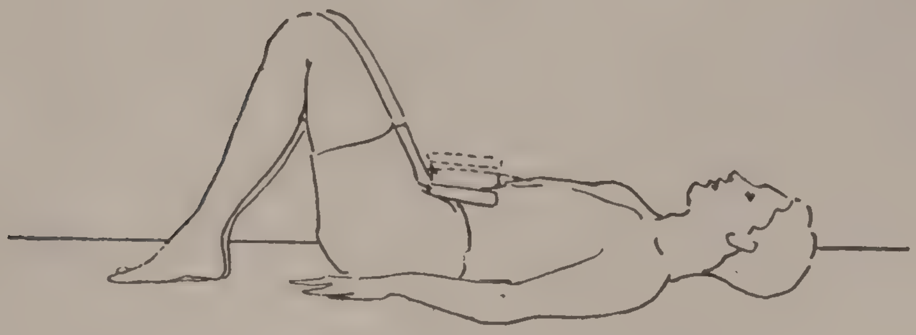


Exercise No. 9—From flat position, hands up straight, legs up straight, knees stiff, toes pointed. Cross hands and legs alternately.

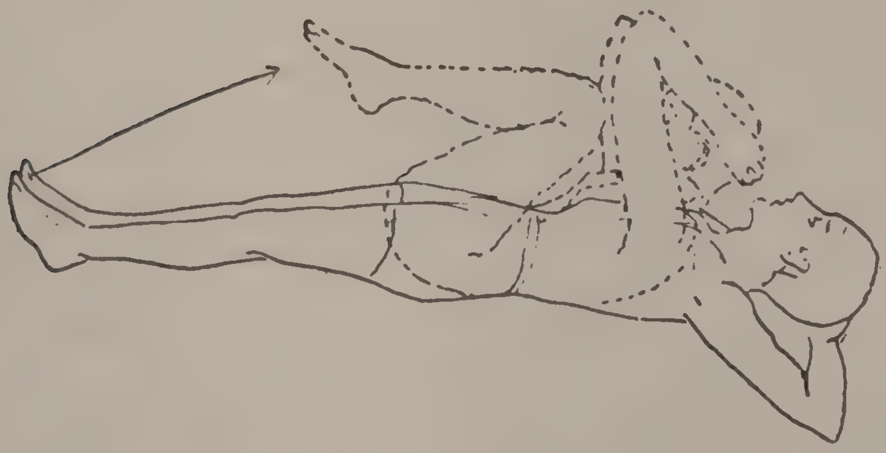
Rest for ten seconds.

SET NO. 2



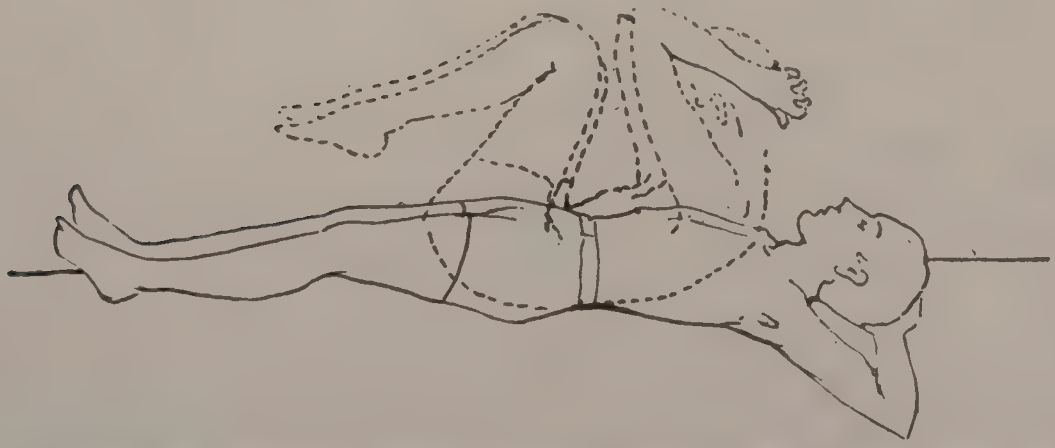


Exercise No. 10—Repeat breathing Exercise No. 1. Repeat Exercise No. 2.

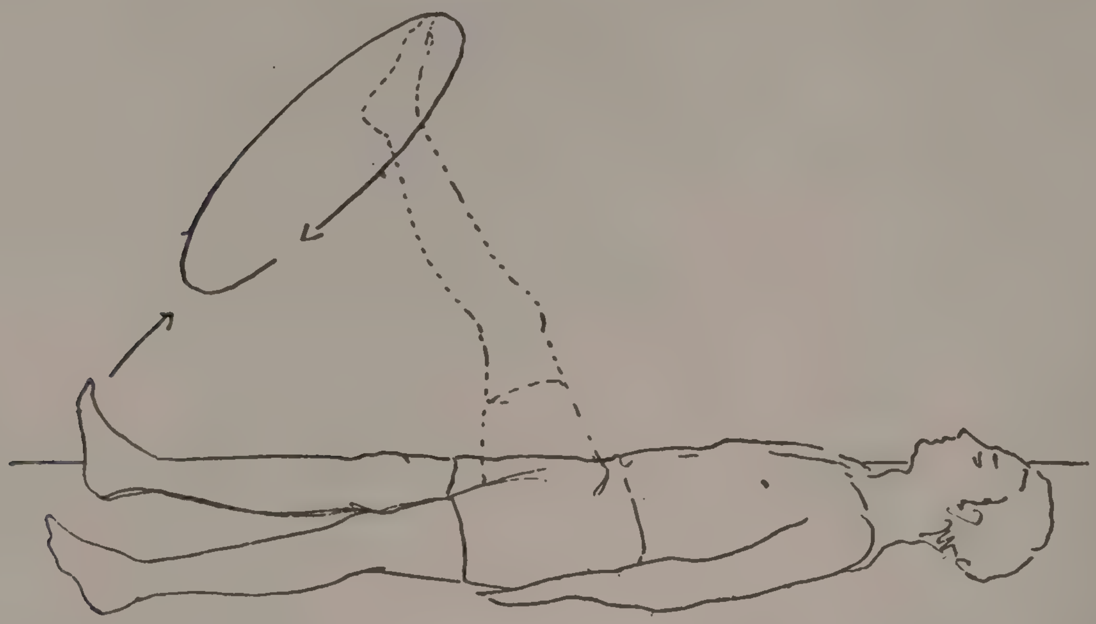


Exercise No. 11—From flat position, legs out straight, hands clasped behind head, raise head and draw up RIGHT knee, trying to touch your chin with your knee.

Exercise No. 12—From flat position, legs out straight, hands clasped behind head, as in No. 11, raise head and LEFT knee, trying to touch your chin with your knee.

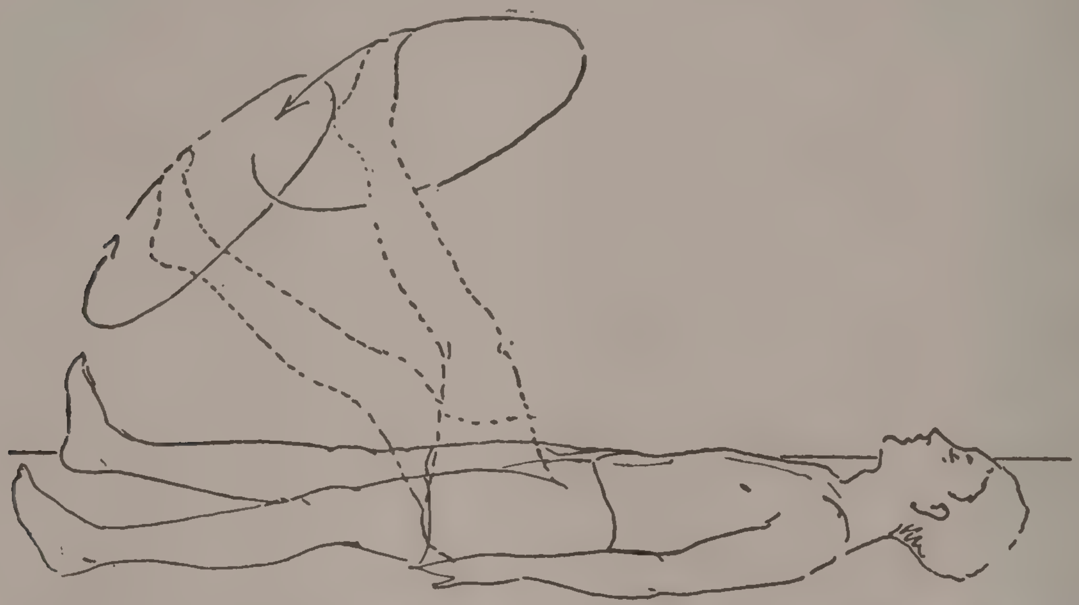


Exercise No. 13—From flat position, hands clasped behind head, raise head and both knees, trying to touch chin with knees.

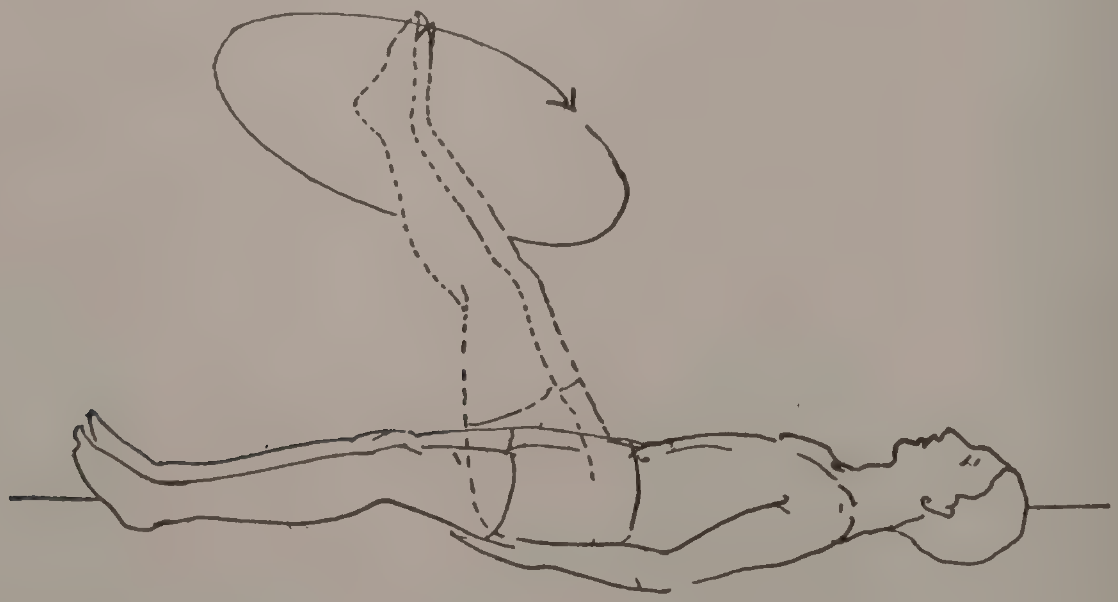


Exercise No. 14—From flat position, hands at sides, legs spread apart, circle right leg. Knees stiff, toe pointed, making a complete circle without touching floor with foot.

Exercise No. 15—From flat position, hands at sides, legs spread apart, as in No. 14, circle left leg. Knee stiff, toe pointed, make a complete circle without touching floor.



Exercise No. 16—From flat position, hands at sides, legs spread apart, raise both legs up and circle them away from each other, making a complete circle without allowing legs to touch the floor. Knees stiff, toes pointed.

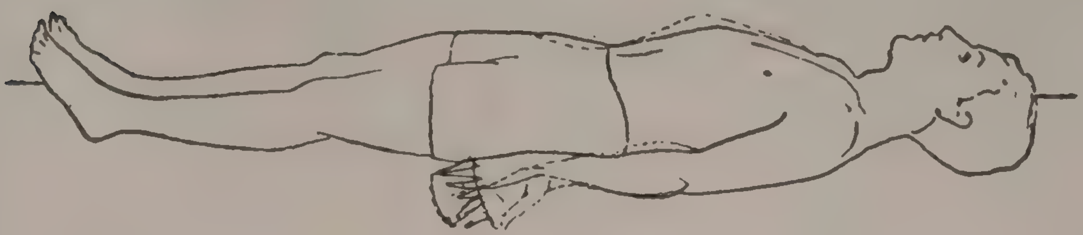


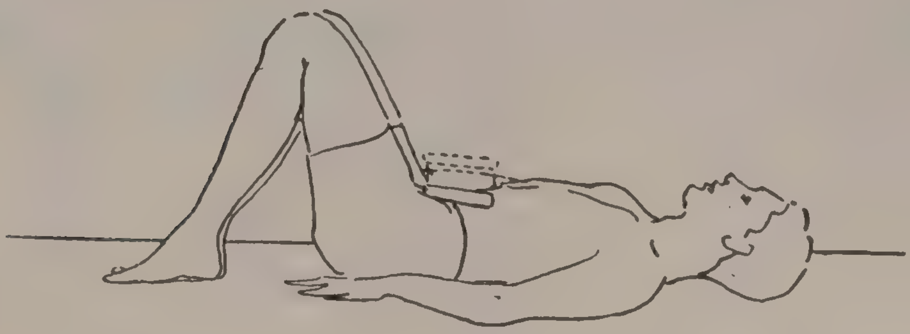
Exercise No. 17—From flat position, hands at sides, circle both legs together to the left, making a complete circle without touching the floor. Keep knees stiff and toes pointed.

Exercise No. 18—From flat position, hands at sides, circle both legs together to the right, making a complete circle without touching the floor, as in No. 17. Keep knees stiff and toes pointed.

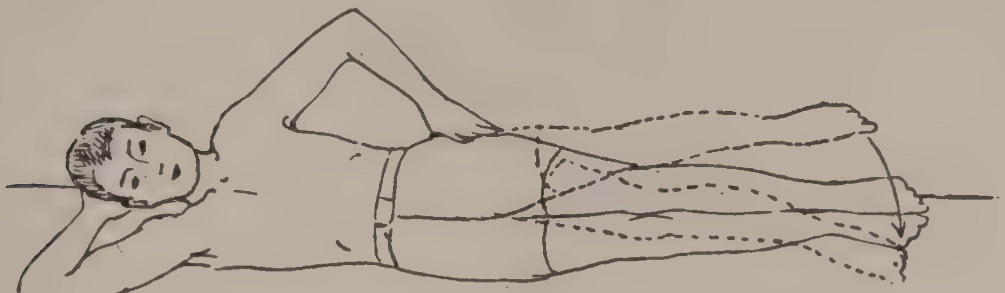
Rest for ten seconds.

SET NO. 3

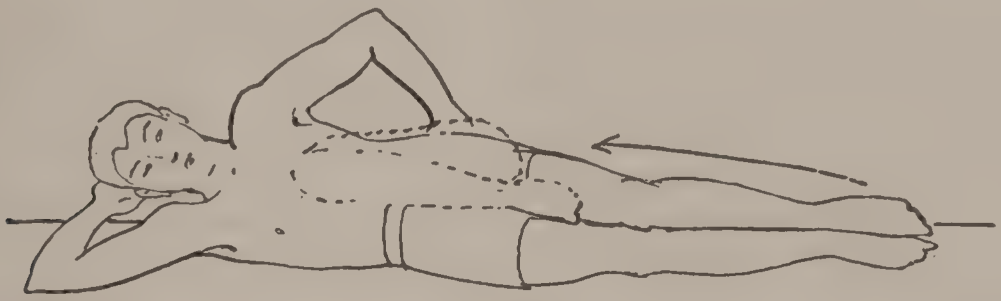




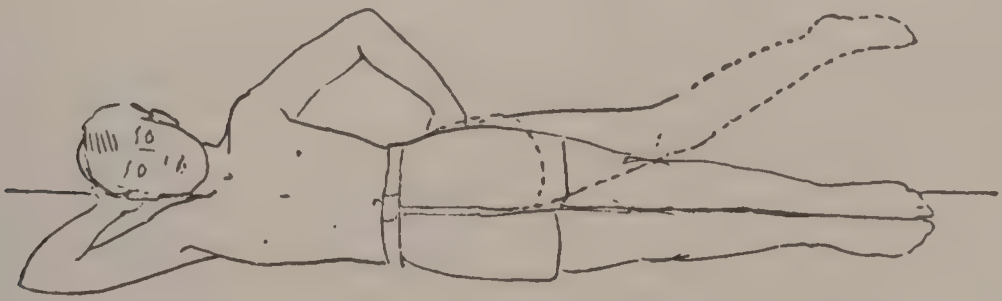
Exercise No. 19—Repeat breathing Exercise No. 1. Repeat Exercise No. 2.



Exercise No. 20—Lie on your right side. Put right hand under head, left hand on hip, swing left leg forward and backward from hip, keeping knee stiff and toes pointed.



Exercise No. 21—Lie on right side, right hand under your head, left hand on hip, draw left knee up to chin, keeping toes pointed.

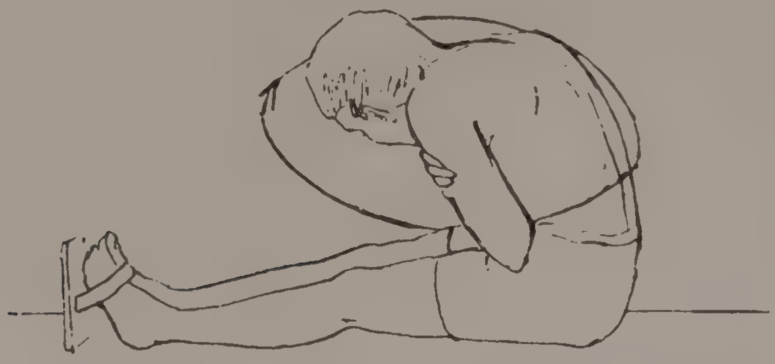


Exercise No. 22—Lie on right side, right hand under your head, left hand on hip, raise and lower leg, keeping knee stiff and toes pointed.

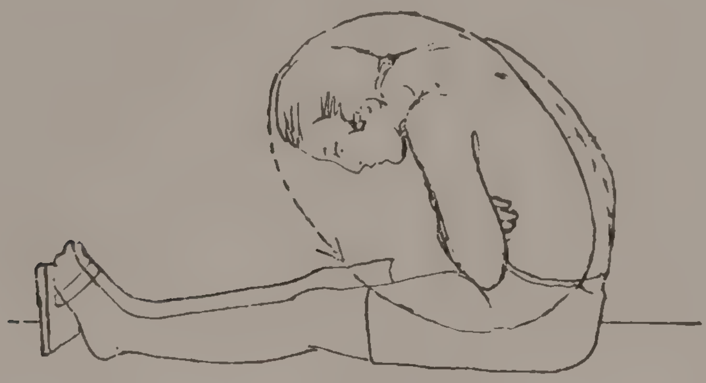
Exercise No. 23—Lie on your left side, as in Exercise No. 20. Put left hand under head, right hand on hip, swing RIGHT leg forward and backward from hip, keeping knee stiff and toes pointed.

Exercise No. 24—Lie on left side, as in Exercise No. 21, left hand under your head, right hand on hip, draw RIGHT knee up to chin, keeping toes pointed.

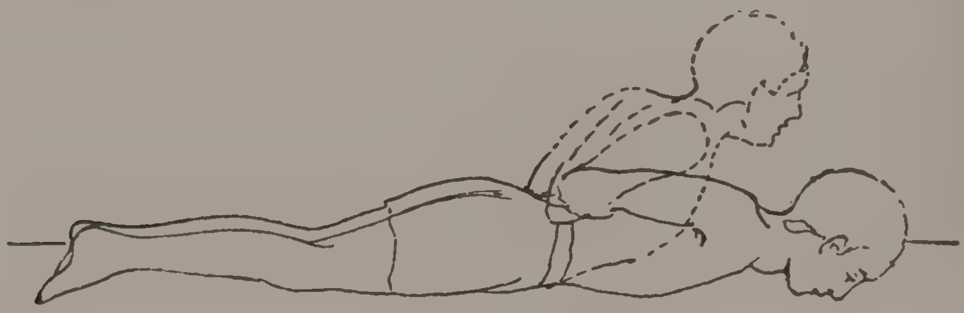
Exercise No. 25—Lie on left side, as in Exercise No. 22, left hand under your head, right hand on hip, raise and lower RIGHT leg, keeping knee stiff, and toes pointed.



Exercise No. 26—From sitting position, place feet under straps, arms folded across chest, circle body to RIGHT.



Exercise No. 27—From sitting position, place feet under straps, arms folded across chest, circle body to LEFT.



Exercise No. 28—Lie flat on stomach. Hands folded behind on the small of the back. Raise head and shoulders towards the ceiling.

ORTHOPEDIC TREATMENT OF VISCEROPTOSIS

The orthopedic treatment of visceroptosis and hypotonicity of the stomach and colon is a subject on which authorities differ widely as to its value, its indications and the particular methods of application.

It is now generally recognized that in visceroptosis we are not dealing with a definite disease. The complicated syndrome that Glenard described and which became associated with his name is a collection of symptoms quite irregular, some of which come about through mechanical embarrassment to the functions of the several organs involved, and some of which are the expressions of vicious circles that extend far afield from the digestive apparatus, including, as they may and generally do, the endocrine system and the sympathetic and systemic nerves, as well as the organs of circulation and respiration. It is, therefore, obviously impossible to formulate any standardized treatment for this complicated condition.

For one patient a rest cure may be indicated, for another corrective exercises may offer the most, and others do best on simple medication. In not a few, a combination of these procedures may be necessary. Nearly all of the patients who suffer from any degree of ptosis of the abdominal organs obtain some relief from the use of corsets, abdominal bandages or trusses. It would be interesting to know just how this relief comes about. The writer has fitted many hundreds of these appliances by the aid of the fluoroscope and rarely has he been able to demonstrate, at the time of fitting at least, any appreciable difference in the level of the stomach or colon due to the support. The intra-abdominal pressure is of course somewhat increased and this may ease tension on the anchorage of the organs, in this way relieving a source of nerve irritation.

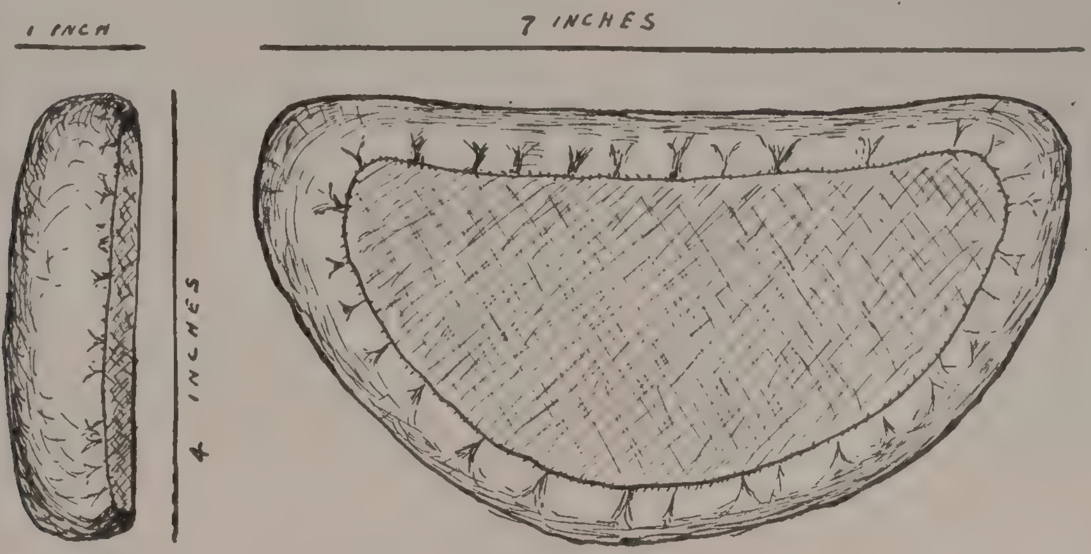


FIG. 2.—SUPPORTING PAD.

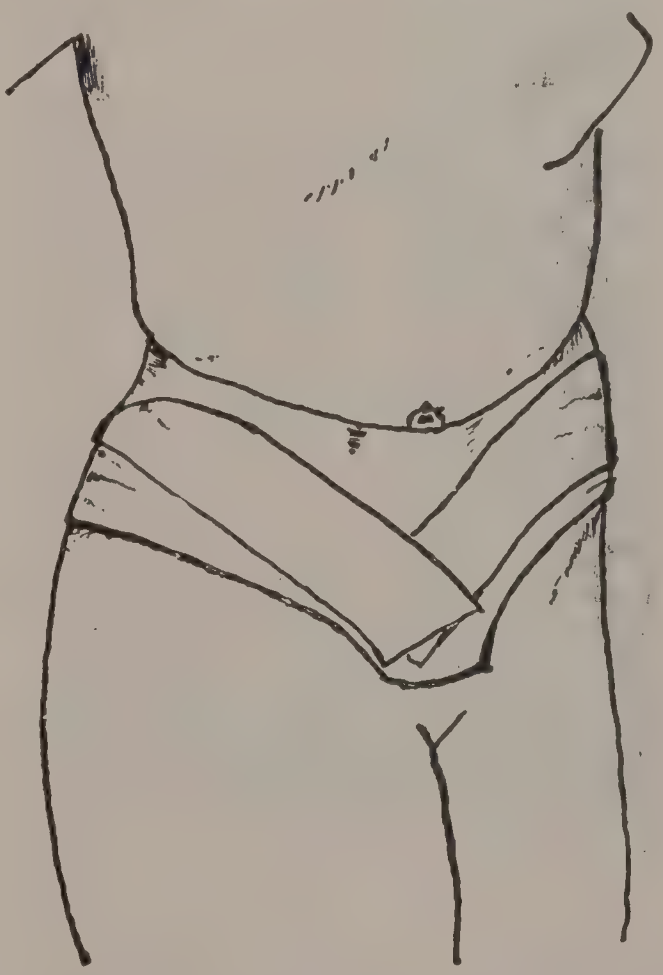


FIG. 3.—ROSE MOLESKIN ADHESIVE BANDAGE.

There is little question but that such support assists in gradually training the movable organs to a higher level and thus to better function. But this does not explain the quick relief so many of these patients obtain when first fitted with support. It seems hardly possible that psychology can explain it all.

The principal requisites for any abdominal supporter are that the pressure exerted should be applied low to the abdominal wall, that the direction of the pressure be back and slightly up, and the supporter so constructed that no counterpressure is brought to bear on the middle or upper parts of the abdomen. These requirements are met in many of the corsets that are advertised for this purpose (Fig. 5), but in some makes the lines of force receive less attention than those of symmetry. But it is not necessary to disregard entirely the requirements of fashion. As a matter of fact, the straight front corset of the present mode is not at all badly designed for purposes of support.

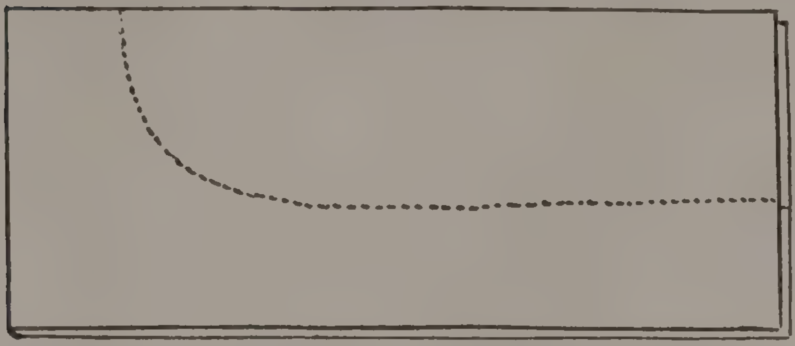


Fig. 4.—Pattern for Cutting Rose Bandage.

Rubber webbing should never be used in corsets or supports that extend above the level of the umbilicus, as pressure above this level, even though it is light, is in the wrong direction and is very apt to offset any beneficial pressure from below. Rubber webbing is not the ideal material for the purpose, even when it is confined to the lower abdomen. It soon loses its elasticity, is not washable, and is uncomfortable because of its weight and the heat it develops.

For thin subjects with scaphoid abdomens and prominent hips, a large pad fitted into the lower part of the support is essential. The pad (Fig. 2) used by the writer is made of wool and cotton felt, reënforced by thin fiber board. It is seven inches wide, four inches high and one inch thick, rounded on its lower border to fit into the space just above the pubis and between the spines of the ilium. For men some form of bandage is usually selected; although rarely, where postural defects are extreme, a modified corset may be necessary. For stout women a corset is best and is usually demanded by these patients for esthetic reasons. Thin women may wear either a bandage or corset, but those with scaphoid abdomens are probably supported best by a corset reënforced by a pad similar to the one described.

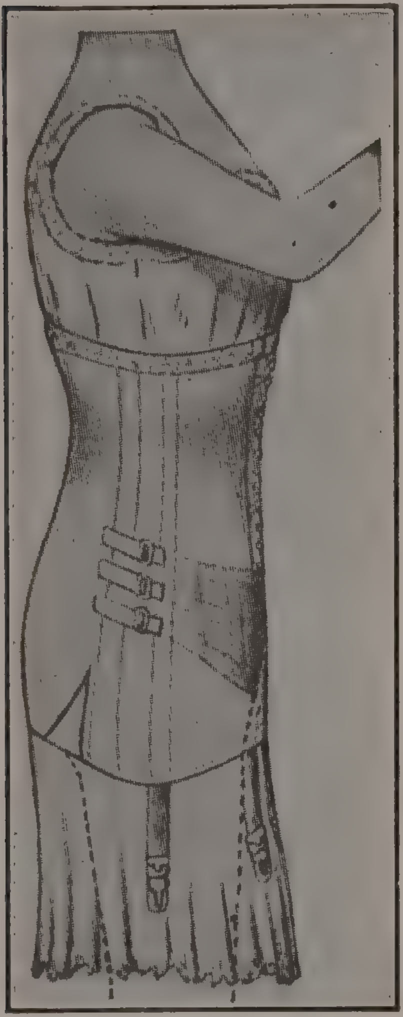


Fig. 5.—A Practical Supporting Corset. (Courtesy of Berger Bros. Co.)

The Rose Bandage.—The Rose moleskin adhesive bandage (Fig. 3) is an excellent form of support for temporary use while waiting for a permanent supporter to be made. It is not possible, however, to keep this on the patient much longer than a week because of skin irritation. Heavy adhesive moleskin is supplied in strips seven inches wide and three feet long. It is to be cut as illustrated (Fig. 4). Before cutting out the pattern the material should be gently warmed and the strip of cheesecloth that protects the adhesive surface removed and then lightly replaced. The plaster is doubled over in the center with the adhesive surfaces folded in. The cutting is then done with one stroke, as illustrated in the drawing by the dotted line (Fig. 4). The cheesecloth is then removed from the three pieces.

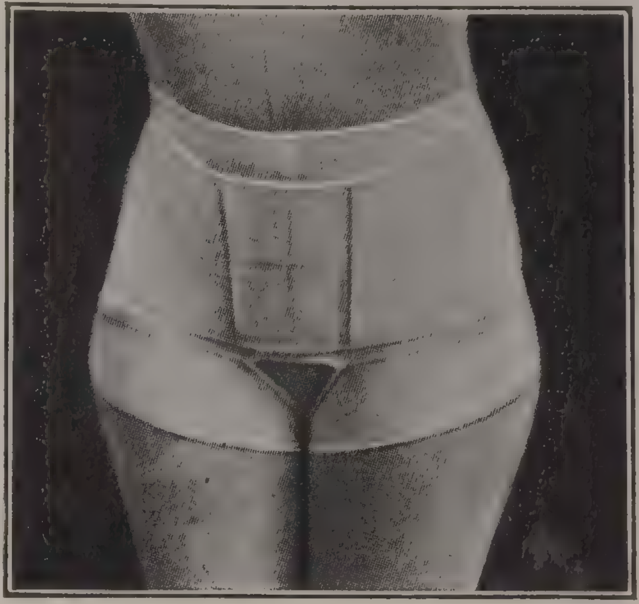


Fig. 6.—A Practical Non-elastic Supporting Abdominal Bandage. (Courtesy of Storm Supporter Co.)

The patient, stripped to below the waist, stands with his back against some low piece of furniture such as a desk, or the footboard of a bed. This should not be higher than the patient's buttocks. Kneeling on the floor in front of the patient, the operator places with his right hand the middle part of the main piece of plaster on the lower part of the abdomen, and with the hand flattened out he makes pressure back and up. Then, reaching around the patient's body with his left hand, he grasps the end of the plaster that is on the patient's left side and pulls it back and adjusts it as tightly as possible as far across the back as it will reach. Then, with the same hand, he takes the other end of the plaster (on the patient's right side) and pulling it back and up, laps it over the other end on the patient's back, constantly keeping his right hand firmly pressed in over the hypogastrium. The reënforcement strips are then placed one on each side, in front, at an angle as illustrated (Fig. 3), the curved border of each pointed up and back. The lower part of the bandage in front is then trimmed so that the pubic hairs are not included any more than is necessary.

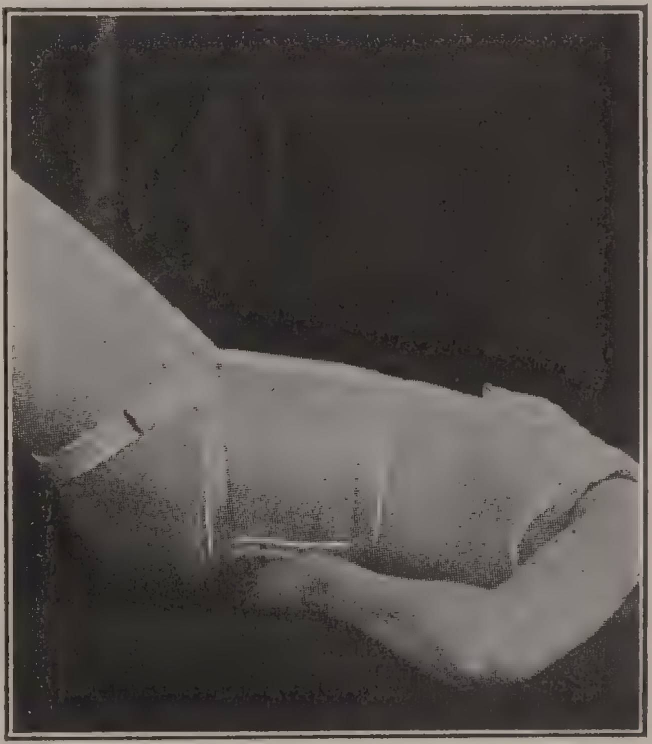


Fig. 6A.—Method of Adjustment, Abdominal Supporting Bandage. (Courtesy of Storm Supporter Co.)

Corsets and Supporters.—In designing or selecting a corset there are several important points to consider. On general principles it is well to have the back built up as high as possible. This arrangement gives support to the spine and helps to keep the corset from riding up; the upper front border should be cut fairly low, especially for those women with large breast development. There is no objection in these cases to lightly adjusted brassières. For thin women the upper front border may be made high enough to partly cover the breasts, but the upper part of these corsets should be made loose. A skirted corset is appreciated by those whose hips and thighs are large, as such skirting helps to keep the corset in place when the patient sits down. Whether the closed-back corset with front lacing is an advantage over the usual form of back-lacing and front-catches is a question. The closed-back corset may be of some use in those cases that require additional support for the spine. Some corset-makers of experience believe that a closed back gives better support to the sacro-iliac joint which so frequently gives trouble to those of the habitus enteropticus, but it is very doubtful if any corset can offer much support to this joint unless it is reënforced by strong, broad straps especially designed for this purpose. When a pad is necessary it should be placed as low as possible; with the patient standing the lower border of the pad should be about a finger's breadth above the pubis.

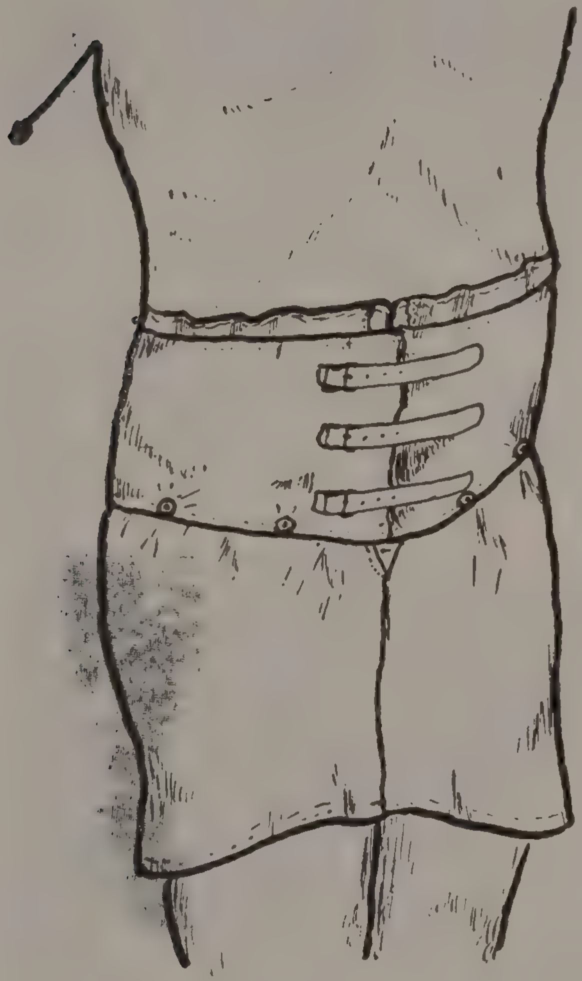


Fig. 7.—A Simple Non-elastic Abdominal Bandage Snap-fastened to a Pair of Athletic Drawers.

There are many makes of bandages to be had (Fig. 6), nearly all of which are satisfactory as abdominal supporters. But some are unnecessarily heavy, stiff or difficult of adjustment. In selecting a bandage these points should be kept in mind. Durability should be sacrificed to lightness, if the requisite pressure can be maintained by the lighter bandage. Patients prefer this even though it may entail more frequent replacements. The writer has used with some success a very light bandage that can be snap-fastened to a pair of athletic drawers (Fig. 7), in this way obviating the rubber perineal straps that are so objectionable. The drawers should fit tightly—a size smaller than those that would ordinarily be worn by the patient.

There are several forms of trusses used for this purpose, but they possess no advantage over the other forms of support and are not so comfortable. They require frequent adjustment that the patient is not competent to attend to.

ESOPHAGEAL, GASTRIC, DUODENAL, AND TRANSINTESTINAL LAVAGE

In esophageal obstruction where there is much dilatation, a regular lavage is not only of considerable comfort to the patient but improvement in the local conditions will frequently result. This is particularly true in cancer. Where there is more or less ulceration, the removal of sloughs and stagnated food at regular intervals is a boon to these sufferers; life can be made more endurable for them and not infrequently prolonged. The regular washing out of a diverticulum is also a useful procedure. When a stenosis is of benign character, the benefit is not always so apparent. But, even here, the soothing of the inflamed parts by lavage is a help. This is true also of the dilatation which may result from cardiospasm. In several such cases the writer has, through lavage, been able to increase the diet and to discontinue dilating instrumentation. It is needless to urge great caution in this procedure. A correct diagnosis is of course essential. Here the X-ray can hardly be dispensed with.

Esophageal Lavage.—The technic of esophageal lavage is simple. The tube should be a soft one, No. 30 French in size, with closed end and large side fenestrations. An old stomach tube that has seen much service and has become flabby and soft through constant boiling meets these requirements. A glass or hard rubber funnel, the lumen of the stem of which is as large or a little larger than the lumen of the tube, is fitted into the end. The distance from the incisors to the most dependent part of the dilatation or sac, having been accurately determined by X-ray and measuring bougie, is plainly marked on the tube.

The patient, properly protected by towels and rubber bib, is seated on the end of a low bench or couch, the operator standing at his right side with his left arm about the patient's head, so that the left hand can be held with the fingers immediately in front of the patient's mouth. With his right hand the operator holds the moistened tube six inches from its distal end. The patient is told to open his mouth widely and to protrude his tongue. The tube is then gently introduced at such an angle that when it strikes the pharyngeal wall it is turned down. The patient is told to close the lips lightly but not the teeth and to go through the motions of swallowing; the operator at the same time gently but quickly passes the tube past the glottis and down into the sac as far as it will go, but in no case beyond the depth-mark on the tube. The patient is then gently pushed back into the supine position and rotated to his right side. The funnel end of the tube is then lowered into the receptacle which has been placed at the side of the bench for the purpose. Too much lowering will cause undue suction and possible injury. If the contents cannot be emptied in this way, or should the tube become clogged, not more than 100 c.c.

of a warm solution of bicarbonate of soda is then poured slowly into the funnel which is raised only an inch or so above the level of the mouth. Again it is lowered for further siphonage. It may be necessary to inject and siphon in this manner many times before one can be sure that the sac is clean, but never more than 100 c.c. should be introduced at a time. Patients can be taught to hold the tube at the proper level by closing the teeth gently on it, thus freeing the operator's left hand. When the solution is finally returned reasonably clear, 20 to 30 c.c. of olive oil mixed with 2 gm. of bismuth subcarbonate should be introduced and the tube quickly withdrawn.

The frequency with which this treatment should be given depends on many conditions. In carcinoma with ulceration, once a day is not too much. Patients sometimes derive so much comfort from it that they practice the washing themselves before taking any food. This of course is not advisable. An intelligent attendant, however, can be taught the technic, but only where the dilatation is not extreme; never when the sac is of a diverticulum and never when there is evidence of much ulceration or of bleeding. In cleaning out a diverticulum, a smaller tube should be used; a very soft rubber catheter, No. 18 French, may be necessary. It may require some manipulation before one can be sure that the sac has been entered; not infrequently the opening into the sac cannot be found. The fluoroscope is here a great aid, but this is only possible in special practice or in hospitals. Smaller amounts of the soda solution are used in these cases, depending on the size of the sac, never more than 50 c.c. at a time and never under any pressure.

This lavage of the esophagus should always be performed with the patient lying on his side, as tension is thus reduced to a minimum. When a patient has learned to regurgitate easily, it is well to have him first lie prone on the bench or couch with his head hanging over the side and thus to empty by gravity as much as possible of the contents before beginning the lavage. This will occasionally save time and the annoyance of having the tube clogged up with mucus, curds or other material. Food should not be allowed for at least an hour after such a lavage. It is very much better to have the lavage done the last thing at night so that the sac is allowed to remain empty until the next morning. Only very small amounts of the blandest liquids are to be given to the patient at the first feeding, following such cleansing. The diet in these cases is discussed elsewhere, but the writer would caution against stimulating foods, even when fluid. Lactose solution in small quantities at frequent intervals is most useful, also diluted cream. Patients themselves soon discover the kind and character of food that will not pass. Olive oil is invaluable. A small quantity should be swallowed before every feeding. Foods should never be ice-cold nor should they be very hot. Charged waters are contraindicated.

Gastric Lavage.—Owing to the more exact methods of diagnosis in these days and to our better understanding of the gastric functions in health and disease, gastric lavage is employed very much less often than it was formerly; in fact, it is seldom indicated except to clean out a stomach decompensated either through lack of tone or obstruction, or in surgical emergencies. It was formerly used in what we now know to be neuroses, such as hyperchlorhydria and hypersecretion. In gastritis it enjoyed a vogue quite as extensive as the nasal douche did in the "nasal catarrh" of the same period. The practice, however, has been more or less abandoned for these troubles except in isolated cases. To employ it for the irregularities of secretion can hardly be excused when we consider that we remove by these washings only the results of an excessive or perverted secretion, that the underlying cause is not, thereby, reached. The temporary relief experienced by these patients is probably largely psychic. In gastritis where there is much mucus production, there is perhaps more of an indication, but even here we may do harm in removing the mucus which nature provides as a protection to the inflamed membrane. These cases can, as a rule, be managed so much better through diet, hygiene and medical means. It is different in phlegmonous and toxic gastritis. Here, there is rational call for the procedure, and it is useful. In extensive carcinomatous ulceration, lavage gives considerable comfort through the removal of sloughs, pus and stagnant food and clotted blood.

When a stomach has become dilated through the deficient motility of atonia, gratifying results through lavage are also possible, which is only somewhat less than that obtained in the evacuation of the retention products of organic obstruction.

Occasionally the reflex vomiting of toxic origin responds to lavage, as in the toxemia of pregnancy. In peptic ulcer, where the lesion is not an obstructing one, it is contra-indicated.

The procedure is simple if carried out with due care and preparation. A nurse or attendant can, however, be trained to carry out the operation when it is necessary to repeat it at frequent intervals.

The tube best suited for gastric lavage is a soft, closed-end tube, No. 30 French in size, with side fenestrations; a glass connector to serve as a window; a short section of additional tubing and a glass funnel, all connected together into a continuous tube approximately 150 cm. long. The patient is seated on a low backless stool with all constricting clothing removed from above the waist, but adequately protected with towels and a rubber apron. A bucket or basin is placed on the floor immediately in front of the patient, and, on a table on one side, a large pitcher of warm soda solution is placed where it can be easily reached.

There is only one right way to pass a stomach tube, and any departure from the method will prove embarrassing. The operator should stand at the patient's right side with his left arm held about the patient's head, so that the fingers of that hand can be held immediately in front of the patient's mouth, to guide the tube and to keep it from being vomited or pulled out. With the right hand, the operator holds the moistened tube five or six inches from its closed end. Oil or other lubricants render a tube less easy to manipulate. The patient, with his head held slightly back, is told to open his mouth widely and to protrude the tongue. The tube is then quickly but gently introduced into the mouth without touching tongue, vault or cheeks, and at such an angle that when it strikes the pharynx it turns down. The patient is told to close the lips gently, but not the teeth, and to make an effort to swallow. At this instant the tube is pushed down past the glottis and quickly into the stomach by a series of quick coördinated movements of the operator's two hands. The usual distance from the incisors to the fundus is 45 cm., but it is well to pass it in 10 to 15 cm. further. With the funnel end held low, the tube is then gently pulled out a short distance, and then back again, the glass window being watched for evidence of contents. If after only a short time of this pulling back and forth of the tube no contents appear, then about 100 c.c. of a warm soda solution are introduced with the funnel held at the level of the mouth or somewhat lower. And then it is raised about a foot aloft. If the solution does not seem to flow in readily, a raising and lowering of the funnel end will usually be sufficient to overcome any stoppage, or the tube itself can be manipulated in and out until this is accomplished. Then, lowering the funnel end, a siphonage is made possible. Until a patient is "tube-broken," it is better not to prolong the operation to completion. Only small quantities of the soda solution should be introduced, never over 200 c.c. at a time.

It is seldom possible to wash a stomach to "crystal clearness," but in cases of obstruction all gross food particles at least should be removed and as little as possible of the solution left in the stomach. The removal of the tube should be accomplished quickly, the tube being pinched tightly to prevent the residue of its contents from being injected from the fenestrations into the larynx as they pass, or from spilling over the patient when the end of the tube is removed from the mouth.

Duodenal Lavage.—Lavage of the duodenum and transintestinal lavage have been practiced for many years. Einhorn seems to have been the pioneer in this field. Rehfuss, Gross, Jutte and others have also repeatedly called attention to the possibilities of this procedure, not only for therapeutic purposes but in diagnosis as well.

Indications.—Lavage of the duodenum is indicated in catarrhal duodenitis and catarrhal jaundice, also in dilatation of the duodenum with partial stasis caused by acute angulation between the second and third portions of the duodenum or further along. This latter condition occurs far more frequently than is commonly supposed, and accounts for some of the obscure cases of periodic vomiting. This acute angulation or kinking can only be diagnosed fluoroscopically, or by means of serial radiography. It is usually caused by the drag of a ptosed colon on the mesacolon, which in turn pulls on the duodenum. The symptoms resulting are not unlike those of the "periodic bilious attack"—a period of constipation, headaches with lassitude, sour eructations, followed by vomiting, the vomitus being of the hypersecretion type. Adhesions involving the duodenum which do not completely occlude it may also cause similar symptoms, but there is less periodicity in these cases.

Transintestinal Lavage.—Transintestinal lavage, or, as Jutte calls it, "the duodenal enema," has been used in treating intestinal toxemia and in the various forms of colitis. The writer has employed this method of intestinal washing and can report some success in well-selected cases.

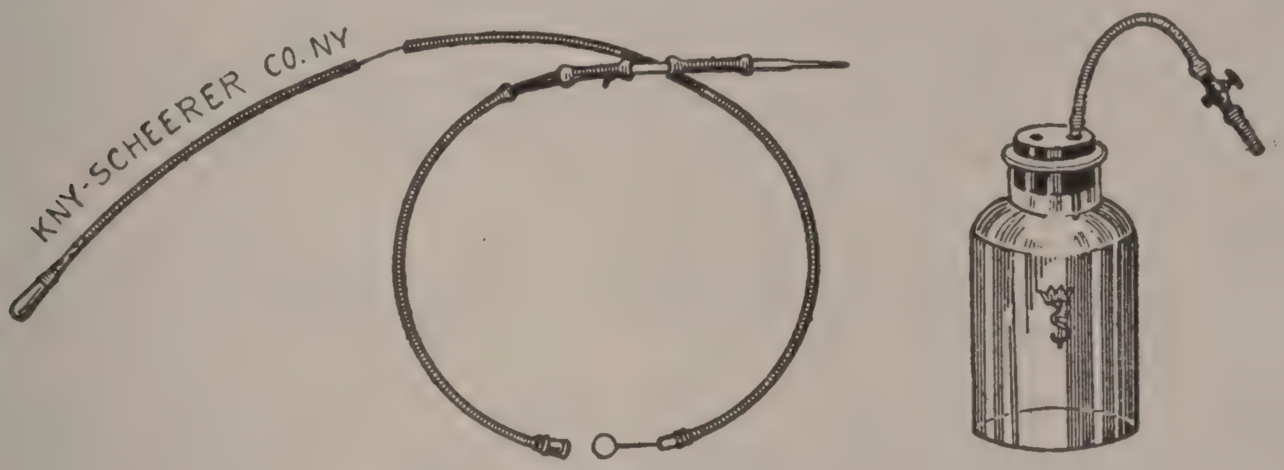


FIG. 8.—THE JUTTE TUBE.

He cannot, however, recommend it for routine practice. The benefit derived is not always in proportion to the inconvenience the patient is put to in expense and in expenditure of time. A regulation of the hygiene in which diet largely enters would seem the better method for the treatment of most of these cases.

Jutte's Method.—The technic for Jutte's method of transintestinal lavage is as follows:

Outfit.—The Jutte tube (Fig. 8) is of the usual duodenal tube caliber; it is fitted with a small closed sinker; fenestrations are punched into the tube itself close to the sinker. The main part of the tube is 75 cm. long; it is connected by a metal socket connector with a section of tube approximately 50 cm. long, and this in turn is fitted into a vacuum suction bottle. The passage of the tube is made easy by a wire obturator carried in the main section of the tube.

This lavage should be given to the patient in a fasting state. The main section of the tube, stiffened by its wire obturator, is passed as an ordinary stomach tube with the patient sitting erect, the obturator being withdrawn as the distal end of the tube enters the stomach. Glycerin applied to the wire facilitates its withdrawal. The patient is then given a swallow or two of water and is placed on his right side on a suitable couch or table, and he is then instructed to swallow the balance of the tube up to the metal connector. The second section of the tube is then joined to this and a gentle suction is started by means of the vacuum bottle. The water that has been swallowed and any fasting gastric contents present are then usually quickly recovered in this manner, and when the tube passes into the duodenum, as it usually does in from five to twenty minutes, the character of the aspirated fluid abruptly changes; it becomes sirupy, is evidently of higher gravity, is more or less cloudy, and occasionally bile-stained. Jutte depends on these changes in character of the aspirated fluid in determining the transit of the tube. The writer has checked up these findings by fluoroscopic observations and has usually found them trustworthy. Change in the reaction of the aspirated fluid is so tardy in appearing that it is useless to depend upon it. When one is reasonably assured that the tube has passed into the duodenum, the patient is given a small meal of crushed crackers and milk to swallow; this serves to close the pylorus. By means of a gravity irrigator the solution to be used is then introduced.

An isotonic solution suggested by Jutte, and which the writer has found satisfactory, is prepared as follows, as described by Jutte:

> "In a busy office it is convenient to keep a stock bottle on hand with grams 90.0 each of sodium chlorid and sodium sulphate dissolved in 1,000 c.c. of water slightly alkaline and filtered through cotton. To 100 c.c. of this solution add 900 c.c. of water at 100° to 110° F. This concentration usually passes along the bowel unabsorbed, but in order to make certain it is often well to add one-half teaspoonful of a 10 per cent alcoholic solution of phenolphthalein, stirring the mixture to prevent precipitation en masse. This standard solution is suitable in most cases, but modifications will suggest themselves according to conditions, for example, addition of quinin in amebic dysentery; salicylic acid, gm. 1.0 in severe fermentation; medicinal soap, gm. 0.5 in disturbed fat digestion and pancreas disease, anthelmintics in intestinal worms, etc."

In the cases of catarrhal duodenitis the writer has found that the addition of 2 gm. of sodium bicarbonate to the liter of the diluted solution just before giving the lavage is an advantage. In these cases, as much as possible of the solution should be removed by means of the suction bottle or aspirating syringe. It is well alternately to flush and to aspirate, injecting each time not more than 200 c.c. A two-way stopcock rigged up between gravity bottle and suction bottle or syringe is a convenience in this maneuver.

In obstinate cases after a number of these lavages have been given without marked improvement, the instillation of a weak solution of silver nitrate may hasten recovery, an effort being made to recover most of this silver solution.

For the treatment of intestinal toxemia and colitis the simple isotonic solution is to be preferred to any combination which includes the so-called intestinal antiseptics. The writer has in these cases discontinued the use of phenolphthalein as it seems unnecessarily to stimulate peristalsis, thereby defeating the purposes of this transintestinal enema. But in appropriate cases the quinin, salicylic acid, medicinal soap and anthelmintics suggested by Jutte may be used.

In giving this transintestinal enema, the solution is allowed to flow in slowly without interruption until all (1 liter) has been thus injected. In most cases the bowels will move copiously an hour or two following the treatment. The frequency of the treatment depends on the individual conditions; if of long standing, three times a week is not too often. As improvement is noted, a gradual lengthening of the intervals between treatments can be arranged, until they are finally discontinued.

GALL-BLADDER DRAINAGE

Meltzer, in 1917, announced his theory of contrary or crossed innervation of the gall-bladder and Oddi's sphincter muscle. In his animal experiments he had discovered that a solution of magnesium sulphate applied directly to the duodenum would cause relaxing of Oddi's sphincter and at the same time a contraction of the gall-bladder muscle. He suggested that this law of crossed innervation might be utilized in practical medicine for draining the gall-bladder.

Lyon perfected a technic for this purpose and two years later in a preliminary paper announced some of the results of his research that were of startling significance. Since then there has been considerable discussion indulged in concerning this theory and the practicability of the method for diagnosis and treatment. Some of the adverse criticism has evidently been founded on inadequate observations or defective technic, or would seem to be the expression of that kind of prejudice that innovations of any sort are apt to engender. But there has also been no little criticism of the method by investigators of undoubted ability and integrity, and the proofs that they submit of the unsoundness of the whole procedure are, to say the least, disconcerting; particularly, when one hears, on the other hand, that men of equal standing and authority have been able, through patient study, to uphold Lyon's contentions and are using the method with considerable success.

The writer has had very little personal experience in the use of this procedure and he has been inclined to doubt its practicability. But recently, at the New York Hospital, a serious attempt has been made to prove or disprove the method, in diagnosis at least, and the results of a limited series of operated cases (12 in all) have been rather favorable. Dr. L. A. Hauser of the house staff in Dr. Conner's service has made a careful study of the Lyon technic and has applied it in these cases. The findings that he obtained in all but 2 of these cases were upheld by the surgeons; in 1 of these cases, there was ample reason for the failure, as the gall-bladder was so packed with stones that no contraction could have occurred and, because of our lack of experience, the findings obtained had been misinterpreted. There were several cases in which it was not possible to pass the tube or to keep it in place long enough to make the necessary observations. No attempt was made in this series to study the specimens bacteriologically. The physical character of the returns and the microscopical appearance are the findings that were relied upon in these diagnoses.

With this practical demonstration in mind, the writer, while still unconvinced as to the value of the procedure in therapeutics, feels that it should not be entirely condemned without further investigation. It is not safe, however, to use the method in place of surgery. The appellation "non-surgical biliary tract drainage" is unfortunate in that it carries with it the suggestion that surgery may be dispensed with in gall-bladder disease. This has, as yet, not been demonstrated and it does not seem likely that it will be, when we consider the principles involved. Granted that by this means the gall-bladder can be made to empty, there is no real drainage established that could possibly be sufficient to overcome an infection, which usually involves the mucosa and even the deeper structures of the gall-bladder. Two years ago the writer made a diagnosis of cholecystitis in the case of a gentleman who had for a number of years suffered from irregular gastro-intestinal symptoms. Some findings in the physical examination also suggested the diagnosis. It was suspected that the coronary vessels were also diseased. Surgery was suggested. At the Mayo Clinic the same opinion was given. The patient, however, while convinced as to the correctness of the diagnosis, was loath to submit to operation, and while at his home in the West was induced to undergo a long course of "non-surgical gall-bladder drainage." After several months of this treatment, with no apparent improvement, he returned to the Mayos and submitted to operation. He died ten days later. The following is an abstract from Dr. W. J. Mayo's report; this is significant:

"The patient died suddenly in an attack of angina pectoris following what appeared to be a very rapid recovery from his operation. I wrote you that the condition found at operation was acute inflammation of the gall-bladder with edematous tissues and several hundred gall-stones. A very marked infection involving the glands led us to hope that this might be the cause of the existing heart condition, and while there was no expectation that the damage already worked could be undone, it did appear reasonable to believe that it could be checked, and the patient given many years of usefulness. Postmortem showed sclerosis of the coronary vessels, but aside from this extreme lesion there was no pathology at any place in the body. It is the belief of those here most competent to judge that, in the absence of all other signs and symptoms of disease, the infection from the gall-bladder was the most probable cause of the heart trouble."

The following are some of the diseases in which this treatment, with reasonable safety, may be given a trial—catarrhal duodenitis, catarrhal jaundice, early choledochitis, early cholangeitis and, as Lyon suggested, acute cholecystitis complicating typhoid fever. It may also prove of value in typhoid fever convalescence when there is continued presence of the Bacillus typhosus in the excretions.

As a means for extending our knowledge in scientific research, this method offers many tempting possibilities. Dr. Lyon summarizes these as follows:

"1. What are the cholagogues? How do they act?

"*a.* By increasing liver secretion of bile or the velocity of its discharge?

"*b.* Do they empty the gall-bladder?

"2. Precursory states and phases of gall-stones and infections, that is, biliary stasis and atony.

"3. Parallel studies on pancreatic secretion, velocity of elaboration of ferments and their discharge. What are the elective pancreatic secretogogues? Have they a place in the prevention and treatment of diabetes?

"4. Extending the scope of chemical investigations into the composition and physical properties of bile."

The apparatus required for drainage of the biliary tract as described and elaborated by Lyon, is a duodenal tube, a 250 c.c. percolator, a 250 c.c. graduate, a 2-ounce glass syringe and five collecting bottles. A complete outfit, according to the Lyon specifications, can be purchased assembled, but a simple working apparatus can easily be fitted up. The most satisfactory tube is the Rehfuss or Lyon modification of the original Einhorn duodenal tube. In these tubes the bulb has longitudinal slits; it is less apt to become plugged by inspissated mucus than the older models. The tube carries markings indicating the approximate distance from teeth to the cardia (42 cm.), the pylorus (58 cm.), and the second portion of the duodenum (75 cm.). An additional 2 feet of tube is attached to facilitate drainage. It is convenient to insert a glass window in this extra tubing in order to observe color changes in the draining bile.

The patient should fast for at least twelve hours before the drainage is performed, although he may drink water. The patient, while sitting erect on a chair or in bed, should swallow the tube to the pylorus mark with the aid of a few sips of water. The stomach should then be washed with water three or four times or until the return is clear. This is accomplished by allowing the water to run in gradually from the percolator and siphoning it into a graduate.

To obtain transit of the bulb into the duodenum, the patient is now placed on his right side with his hips somewhat elevated and the legs flexed slightly on the trunk. He swallows the tube slowly to the last mark, taking at least twenty minutes to do this. The passage of the bulb into the duodenum is indicated by a change in consistence of the fluid drained and by the presence of the so-called "duodenum tug," the change in the reaction from acid to alkaline and by the non-return of fluids taken by mouth. If doubt exists as to the position of the tube it is well to determine its position by fluoroscopy, but this is usually not necessary. It ordinarily takes from twenty minutes to forty minutes for the bulb to reach the duodenum. Should it be impossible to pass the tube beyond the pylorus it is worth while to attempt a relaxation of the sphincter by instilling 20 to 30 minims of Tr. belladonna diluted in 100 c.c. of water.

Being assured that the tube is in the duodenum, we are now ready to induce a flow of bile. This is accomplished by instilling 60 c.c. of a 33⅓ per cent solution of magnesium sulphate by means of the large glass syringe or by gravity. Following the injection, the tube is closed for about three minutes and the solution then allowed to drain. In this way more than half of the magnesium sulphate can usually be recovered. According to Meltzer's "law of contrary or crossed innervation," stimulation of the duodenal mucosa by a topical application of a solution of magnesium sulphate will cause a relaxing of Oddi's sphincter and a contraction of the gall-bladder muscle. Through this physiological mechanism bile begins to flow through the tube following a regular sequence of color changes. The first, the "A" bile, is light golden yellow; according to Lyon it represents the common duct bile. Normally this is followed by the drainage of about 75 c.c. of a brown or greenish brown bile, the so-called "B" bile (bile from gall-bladder, Lyon). After all the dark-colored bile has been drained, a large amount of a light golden-colored "C" bile comes through the tube. This Lyon believes is the freshly secreted hepatic bile. Should one stimulation of magnesium sulphate fail to bring a free flow of bile, it is well to stimulate a second time with a smaller amount of the solution, from 40 to 50 c.c.

After the drainage, the duodenum is disinfected with a solution of potassium permanganate in a dilution of 1:10,000. This should be immediately siphoned off to prevent undue irritation of the duodenum and a duodenal enema of 250 c.c. of Ringer solution (NaCl, 0.7 per cent; KCl, 0.03 per cent; CaCl, 0.025 per cent) given at a temperature of 105° at a rate not to exceed 100 c.c. in five minutes. This enema may be reënforced with a .5 to 1 per cent solution of sodium sulphate, the amount used depending upon how much magnesium sulphate was recovered from that used in the drainage stimulations. This usually causes a free bowel movement in fifteen to twenty minutes. After the tube has been removed the patient should be given a cup of bouillon and crackers to tide over any faintness which he may experience.

In most cases it will be sufficient to drain the biliary tract every three or four days for the first two or three weeks; the interval between drainages may then be prolonged to six or seven days, depending upon the relief of symptoms and on the patient's condition.

DILATATION OF ESOPHAGEAL STRICTURES AND SPASM

The plight of the patient who realizes that he is suffering from stenosis of the esophagus is one of the most pathetic with which we are called upon to deal. The knowledge that one suffers from any grave disease is always alarming and damaging to one's morale. The human animal, however, when confronted with such problems usually becomes adjusted very quickly and Nature plays her hand so subtly that hope is seldom entirely abandoned by the most obviously doomed. But those who suffer progressive stenosis of the esophagus are usually from the beginning conscious of the hopelessness of their situation. Even the most ignorant realize the futility of surgery and they succumb early to the panic that the prospect of slow starvation excites. Any relief, therefore, that can be afforded these sufferers is well worth striving for. But this is a field that all are not privileged to work in.

Palliative Measures.—A great deal can be accomplished by diet, by esophageal lavage, rectal feeding and such general measures. The dilatation and maintenance of an adequate patency of the esophagus, however, is, or should be, left to those of special training and experience. To emphasize this it is only necessary to call attention to the fact that a large majority of the sudden deaths due to dilatation of the esophagus have occurred in physicians' private offices, and the number of such accidents is not inconsiderable. It is needless to add that all reasonable precautions had been taken in many of these cases, that the unfortunate accidents could not have been attributed always to a lack of skill of the operators, but often to complications which could not be foreseen. But inaccurate and incomplete diagnoses and clumsy antiquated methods have brought humiliation and trouble to many a venturesome practitioner. The writer would caution all who are not specially equipped to make these diagnoses, and who have not acquired the necessary skill, to refrain from attempting any dilatation of the esophagus.

Important as it is, it would be impossible to give in this place any detailed description of the diagnostic procedures necessary before instrumentation is justifiable in disease of the esophagus. A history may, and usually does, make a diagnosis of stenosis obvious, or the passage of a stomach tube in routine practice may call attention to some impediment; and, with our suspicions aroused as to the possibility of a stenosing lesion, carefully passed olive-tipped sounds may confirm our fears. But, until we have thoroughly studied such cases radiographically, we are not in a position to proceed with dilatation or any form of treatment other than the simple palliative measures already mentioned.

X-ray Films Necessary in Diagnosis.—By means of the fluoroscope we are able to determine the site of a stenosis or spasm and the degree of dilatation that has taken place above the lesion. But we cannot always thus differentiate between cicatricial and simple stricture and carcinomatous obstruction. Films are here necessary, not only for purposes of accurate diagnosis but also in order to plan dilating operations. We have to differentiate between simple stenosis, cancer, diverticulum, impacted foreign bodies, spasm and pressure from without.

Bougies.—In simple stricture where compensatory dilatation is not extreme and the narrowing occurs in the most dependent part of the dilated section, and in the absence of pouching, a gradual dilatation by means of the Deboulet French gum bougies is comparatively safe and simple. Even in carcinomatous obstruction, if these conditions obtain and it can be determined that the narrow channel is not irregular, it would be worth while to try this simple procedure before resorting to more elaborate instrumentation. But one should be extremely careful in such cases, remembering always that cancer tissue is friable and irregularly so, that soft ulcerated areas cannot be told from firm tissue, either by sound-touch or X-ray shadows. The use of the fluoroscope is of great help in the passage of these sounds.

There is nothing difficult in the passage of a dilating bougie. The patient should not eat within several hours previous to the treatment. If there is any retention, a small preparatory lavage is indicated. The bougie should be gently warmed to insure pliability of the long narrow tip and well lubricated with olive oil. The passage is accomplished in the same manner as the passage of a stomach tube, except that the patient's head should be held back as far as possible to decrease the angulation at the pharynx between the buccal cavity and the esophagus. At the first indication of resistance to the progress of the bougie, pressure is released and the instrument is withdrawn a short distance and then pushed on with only the gentlest pressure. If repeated efforts to pass beyond the apparent obstruction are unsuccessful, this kind of treatment should be abandoned as not practical for that particular case and a safer method of mechanical dilatation attempted.

Filiform Sounds.—The use of filiform sounds that under manipulation seek out the passage and, when passed completely through, act as guides for olive-tipped dilators of different sizes, is one of the simplest procedures, but one that is not always reliable or entirely devoid of danger. There are several systems that utilize the thread-guide principle. They differ somewhat in technic and construction of apparatus but are essentially similar. Sippy's is perhaps the best known of these methods and seems to include the desirable features of the others. The one serious objection to this and the other methods that utilize the thread guide is in the knotting or tangling of the thread which occurs not infrequently. Some patients find the thread difficult to swallow and unpleasant to retain in place overnight.

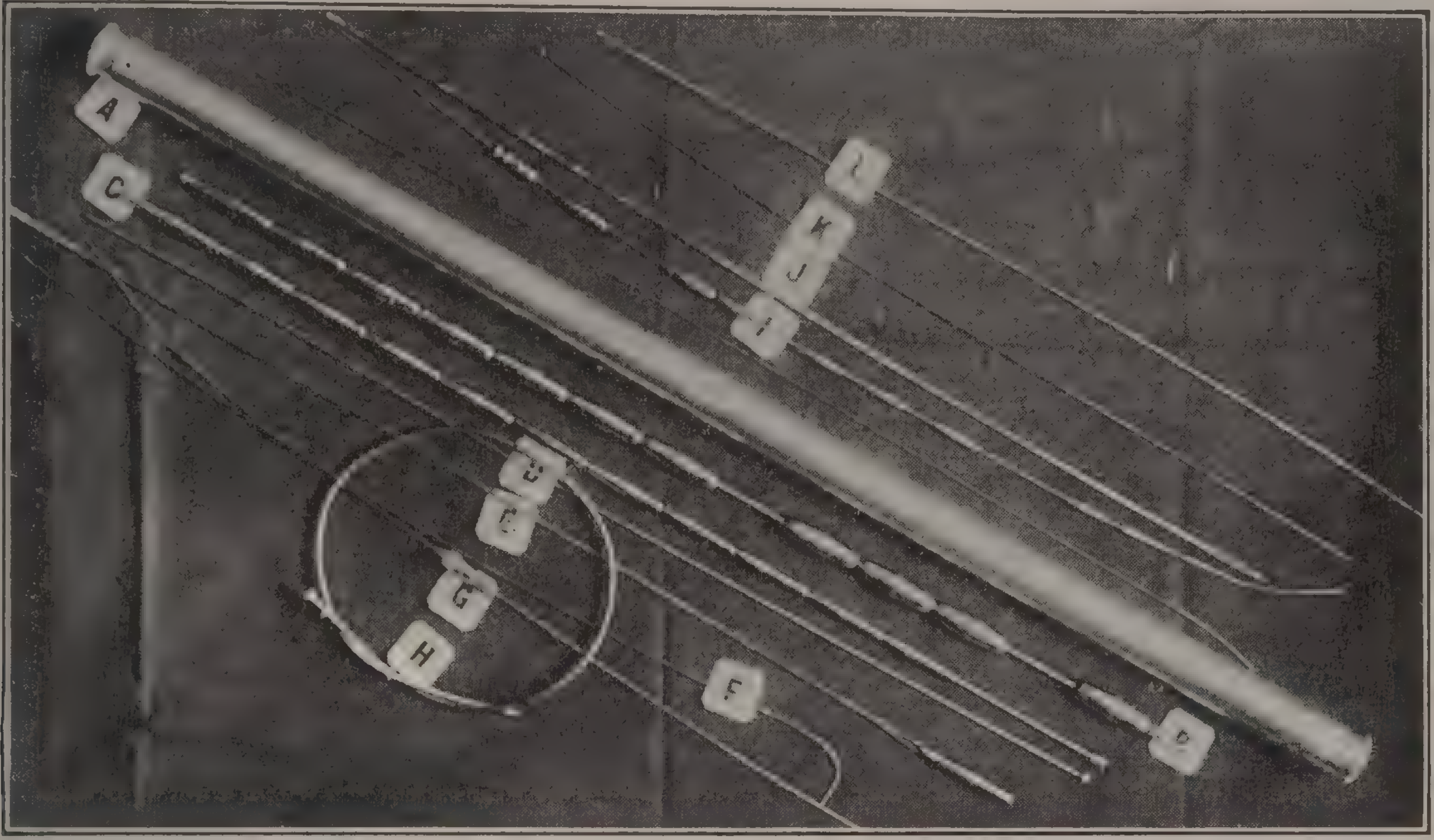


Fig. 9.—Dr. A. C. Crump's Instruments for Dilatation of Esophageal Stricture.

A. Aluminum Instrument Case.

B, C, I. Olives for treatment of cicatricial stricture in size from No. 10 French to No. 40 French.

E. Staff with olive attached, staff showing forked end, allowing passage of guide wire. Staff 20 inches (50 cm).

F. "Flexible tipped piano wire."

G. "Chuck."

H. "Carrier 18."

K. "Guide wire 24."

L. "Guide wire" with perforated small olivary tip for passing on silk thread.

Crump's Instrument.—The Crump apparatus (Fig. 9) appeals to the writer as the most practical so far devised; it is expensive and difficult to obtain, but its simplicity of operation and correct principles should commend it to those who are interested in this special practice. The principle of its operation is similar to that of the filiform but is very much safer and more practical (Fig. 10). A flexible tipped piano wire in a flexible carrier is passed to the site of the obstruction. The carrier is then withdrawn about two inches and a chuck or weight is then temporarily attached to the outside or mouth end of the wire, and by this means the wire is gently rotated. This imparts a corkscrewlike motion to the flexible tip of the wire which is free to seek out the opening and, as it enters this, the same rotary motion and very slight pressure on the chuck propels it through. The carrier is then passed on through over the wire, until it is stopped by another shoulder or irregularity, when the same maneuver is repeated, until one is sure that all of the obstruction has been passed. The chuck is then removed from the wire and the carrier withdrawn, leaving the wire in place to act as a guide for the olives. Some special mention should be made of the olives Dr. Crump uses, as they differ from those usually employed. The illustration will show that they are long and therefore the degree of slant is very much less than in the commonly used, almost round olive. This insures a more gradual and safer dilatation and the dilating force is applied both on introduction and withdrawal. The flexible staff on which the olives are screwed is also an improvement in that it is provided with a forked-end arrangement which permits a centering of the olive on the staff and a free passage of the guide wire.

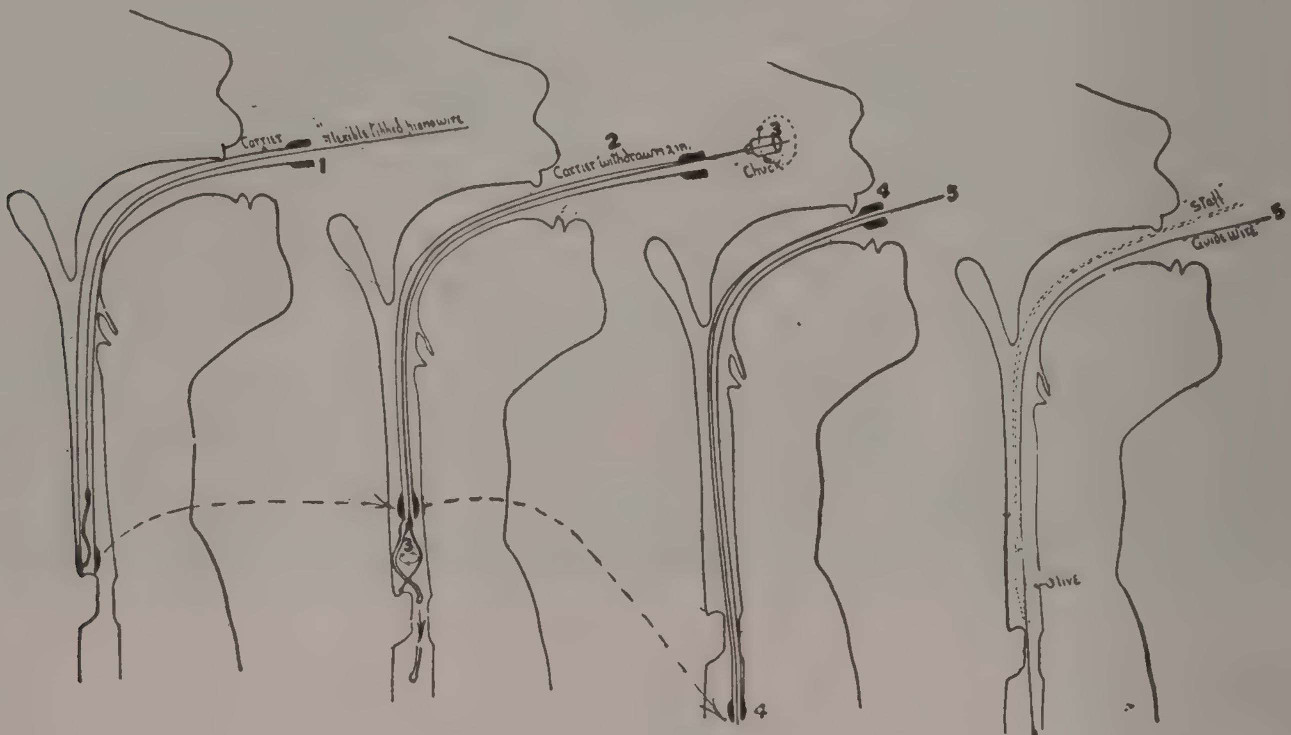


Fig. 10.—Crump's Method of Dilating an Esophageal Stricture.

Bag Dilators.—The writer has had no personal experience with any of the air-bag or water-bag dilators and does not feel competent to discuss the technic of this method. He believes that it is not a safe procedure, as the dilating force cannot be confined or adequately regulated.

Frequency of Treatments.—There can be no fixed rule for the frequency of dilating treatments. In the cicatricial strictures, the intervals between dilatations should not be longer than a week. In the beginning, three treatments a week is not too often, unless this causes undue irritation. As one progresses in a case one can usually determine the amount of resistance to be overcome and how soon the stretching effect wears off. The succeeding dilatations should be so planned that little of this effect is lost, that each dilatation leaves the canal a little wider than the preceding treatment.

In cancer the treatments should be given only often enough to insure some patency of the canal. If these patients can be made to take soft foods, there is little use in persisting with the treatments. Lavage is always useful in these cases.

When spasm is the cause of an obstruction, the treatments should be given at first daily, and the size of the olives or bougies rapidly increased. It is well, however, to occasionally stop the dilatation in these cases for a few days to a week to observe the effect of the treatment.

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THE INFECTIOUS DISEASES

INFECTIONS DUE TO BACILLI

CHAPTER XII

TYPHOID FEVER

Frederick C. Shattuck, Roger I. Lee and Frederick F. Russell

PROPHYLAXIS

Frederick C. Shattuck

Revised by Roger I. Lee

So much do we know of the causative agent of typhoid fever, of the means by which the disease is spread, and of the way in which such spread may be prevented, that it is quite conceivable that, within a reasonable time, the disease should, in the human, not in the geologic, sense, be exterminated from the earth—that the Bacillus typhosus should become as extinct as the great auk. A consummation so devoutly to be wished is, however, easier to conceive than to realize in fact. By far the larger part of the inhabited earth is occupied by people who must long remain backward from a sanitary point of view. The ease and rapidity of intercommunication between the uttermost parts of the earth are constantly growing. Among the most enlightened peoples the by-product of those whose minds seem to be as impenetrable to the evidence of science and to common sense as is lead to the X-ray—cranks, in short—seems to be fostered rather than eliminated by civilization. The prevention of smallpox is a simple problem as compared with that of typhoid fever, and is more than a century old; but ignorance and prejudice still live, even among the most advanced peoples, and the time when vaccination for smallpox shall become a lost art is not in sight. Nevertheless, the steady reduction in the incidence of typhoid fever in all civilized communities is perhaps the most gratifying achievement of sanitary science. No longer are our hospital wards given over almost exclusively to the treatment of typhoid fever after the first of August. One hears not infrequently the complaint that it is hard to get cases of typhoid fever for the necessary instruction of students. It is well so.

Vehicles of Transmission.—There is general agreement that the typhoid bacillus, in order to cause disease, must be taken in through the mouth and swallowed. It is evident therefore that the usual method of transmission is by food and drink which have been contaminated by typhoid bacilli. There is abundant evidence from the repeated occurrence of typhoid fever in individuals caring for typhoid fever patients that the typhoid bacteria may enter the human body as a result of inadequate precautions in regard to the washing of the hands, etc. Epidemiological studies in typhoid fever have given us much information as to the method of spread. However, we still need information as to the exact degree of the importance of flies, of typhoid carriers, and certain other aspects of the epidemiology of typhoid fever. In general, the pollution of a water supply is the cause of the majority of cases of typhoid fever. The next considerable vehicle is polluted milk, which may be polluted by water or by human carriers. Very much less important, but still a considerable factor in the total number of cases, are those cases which have been infected by typhoid carriers. The typhoid carriers must pollute a food in which the typhoid bacilli can survive and multiply, and the food must not, of course, be cooked after pollution. The most famous typhoid carrier is the well-authenticated case of Typhoid Mary.

Oysters at one time were found to be connected with typhoid epidemics, but adequate sanitary regulations have largely eliminated the oyster as a source of typhoid fever.[1]

Of very much less importance, in the total number of cases, are those cases contracted in the care of typhoid fever patients. Those cases are unquestionably due to crimes of sanitary technic, and are not always to be wondered at when one considers the conditions under which typhoid patients are sometimes cared for. Even in the best regulated hospitals, the incidence of typhoid fever among nurses was not always controlled by routine sanitary technic, until typhoid vaccination was added.

The actual rôle of flies in the spread of typhoid fever has as yet not been determined. From the available evidence it would appear that it is perfectly possible for flies to act as a vehicle of transmission of typhoid fever, but it seems unlikely that flies are a very important transmitting agent.[2]

How many people have typhoid without knowing it? Any one of these may become a typhoid carrier and an innocent source of many other cases, even if every case of typhoid coming under observation is promptly recognized and properly treated. Physicians remote from centers of population may have no outside facilities for determining whether a patient after recovery becomes a carrier or not. They cannot, at present at least, be expected to have both the knowledge and equipment necessary to settle the questions themselves. No typhoid patient is discharged from the Massachusetts General, and doubtless the same rule holds with most similar hospitals, unless cultures of the urine and stools are negative. The difficulties inherent in the application of such a rule in private practice, especially among those of moderate or slender means, are patent, though not insuperable, provided there be real coöperation of the profession, active boards of health properly furnished with both money and power, and the public. Too many health boards are such only in name, naked, impotent, or both. Heavy penalties for failure to report cases promptly may help the cause, but more reliance is to be placed on the enlightened conscience and mind of the physician than on his fear of punishment.

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[1] During the past summer a small group of cases in New Haven was pretty definitely traced to contaminated clams.—Editor.

[2] This is undoubtedly true of the conditions of ordinary civil life. In military encampments the conditions favoring a spread of the disease by flies are much more likely to be present.—Editor.

Apparently 4 to 5 per cent of typhoid fever patients are carriers in their early convalescence. This percentage slowly diminishes. The convalescent carrier may become a permanent chronic carrier.

The occurrence of typhoid bacilli in the stools of individuals who do not come down with typhoid fever is a possibility, the thorough extent of which has not yet been worked out. In other words, there are certain observations which indicate that individuals may receive typhoid bacilli, but that the typhoid bacilli may not be able to produce the disease, and the individual gets rid of these bacilli in varying lengths of time.

It has been estimated that the total percentage of typhoid carriers in the ordinary community may be 0.3 per cent.

While it is true that a small number of typhoid bacilli withstand prolonged freezing, it seems to be established that the risk of the spread of the disease through ice is not sufficient to warrant unusual precautions.

Broadly speaking, the essential difficulty in this country in the control of typhoid fever is the unsettled state of the water and sewerage problems in many of our growing communities. There is great need of the realization on the part of the communities at large that the installation of a water system carries with it attendant dangers. It is not sufficient that sewage material is carried off by water, it is necessary to know the ultimate disposal of such sewage material. It is mainly in the transition stage in which prosperous communities find themselves when they are outgrowing their systems of water supplies and sewage disposal that typhoid fever occurs in a disgraceful degree. Unless there is everlasting sanitary vigilance, the sanitary disasters which were so common in the Spanish-American War will tend to visit rapidly growing communities as those disasters visited the mushroom cities of soldiers, no matter where located, in 1898.

Vaccination.[3]—A further means of prevention of typhoid fever is antityphoid vaccination. This procedure has now been under scrutiny for twenty years, and it is possible to speak in rather positive although somewhat general terms concerning its value. Wherever there have been comparable figures, these figures have shown a reduced incidence of typhoid fever and reduced mortality rate among those who acquired typhoid fever, in the vaccinated group as contrasted with the unvaccinated group. In the recent typhoid epidemic in Salem, Ohio, only three or 1.4 per cent of the two hundred and ten ex-service men in the town had the disease, while 12.5 per cent of the women of the same age group contracted typhoid fever. These figures are illustrative of general figures which may be obtained. The interesting feature of these particular figures is that they show the protection afforded by typhoid vaccination among the civil population.

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[3] This subject is considered in greater detail in Colonel Russell's section of this chapter.

It seems to be certain that typhoid vaccination does not afford complete protection to 100 per cent of individuals at any time after the inoculation. Typhoid vaccination is effective for a widely varying length of time, and we have no bacteriological or biological criterion as to the existence or the duration of the protection afforded by the antityphoid inoculation. This protection seems to be much more complete during the first year, and, on the whole, revaccination is to be advised at the end of the first year, and apparently again at the end of two more years. While previous vaccination against typhoid fever apparently decreases the mortality from the disease, it does not modify its course in any striking fashion. Shortly after the introduction of vaccination against typhoid fever, it was felt that the typhoid fever in the vaccinated ran a peculiar course, presumably unlike that of typhoid fever. Collected observations, however, have on the whole rather failed to substantiate the view that typhoid, although milder, is a different disease after vaccination. These same variations in the course of disease are seen without vaccination as well as after it. It is perfectly well recognized that typhoid fever may run a very atypical course.

Technic of Typhoid Vaccination.—Antityphoid vaccine is now prepared and furnished by many health authorities and by the usual drug houses. The vaccine consists of a killed culture of typhoid bacilli standardized by count. Adequate directions are nearly always given on the preparations. The date of preparation should be carefully observed. The materials should be used relatively fresh, that is, within a few months. It is preferable to use the material within two months, although apparently good results can be obtained within six months of the time of preparation. It is likely that the material will last more or less indefinitely when kept under ideal conditions, that is to say sterile, in the dark and in the cold. Such conditions are not usually obtained, and this fact emphasizes the desirability of using fresh material. Typhoid vaccine may be given alone. It is more customary to add paratyphoid A and B to the typhoid bacilli. The usual dosage is for the first dose five hundred million of dead typhoid bacilli, plus two hundred and fifty million each of paratyphoid A and paratyphoid B, and the dose is doubled for the second and third doses. The material is usually so put up that the first dose consists of ½ c.c. (7½ minims) and the second and third doses of 1 c.c. (15 minims). The interval between injections should be from seven to ten days. The vaccine is injected with an ordinary subcutaneous syringe which is sterilized in the usual way, and the skin is sterilized by alcohol or iodin. The injection is preferably made rather deep into the muscles in the region of the deltoid. Reaction is seldom severe, but in individual cases there may be redness and pain about the site of the inoculation, and fever and malaise for twenty-four hours. The occurrence of one severe reaction does not necessarily mean that the other reactions of the series will be also severe. In case an individual has very severe reactions on more than one injection in a series, it is probably certain that that individual is already protected against typhoid fever, and that further inoculations are not expedient. In general, if the inoculation is given in the late afternoon, whatever reaction occurs takes place during sleep at night, and only a small percentage of individuals will find themselves incapacitated for work, and that only for a very short time.

Antityphoid vaccination is to be particularly recommended for all nurses in those hospitals which take care of typhoid fever patients, and for all individuals who are likely to drink water from uncertain sources. The last group includes particularly those who travel for business, or those who expect to take a prolonged vacation in out-of-the-way places. Inasmuch as the most visited countries in Europe have on the whole rather less typhoid fever than the United States, it is more logical to advise the person about to travel in the United States to be vaccinated against typhoid fever, than the person about to travel abroad.

Prevention of Extension.—The principles underlying the prevention of the extension of the disease from the individual patient to healthy people are clear and fixed. Their application to the special case must vary in detail with the circumstances under which said case is cared for.

The chief danger lies in the feces and urine, their accessibility to flies, and in the bed and body linen liable to be soiled; but all secretions and excretions are possible sources of danger. With proper precautions isolation of patients is not necessary, and no valid objection can be raised to their care in the general medical wards of a hospital. It is well, for convenience, to group the typhoid cases under a special nurse or nurses.

Although Boston, as a seaport town, discharges its sewage into salt water and only on the first half of the ebb tide, the following rules are observed in the Massachusetts General Hospital, and are in essence those which should obtain in any large institution:

Feces.—The bed-pan is emptied and washed out into a special hopper, the outlet of which has been previously closed. The cover is shut down and steam allowed to circulate in a jacket at the bottom of the hopper. The contents are thus quickly brought to the boiling point and there maintained for five minutes.

Bed-pans and urinals are sterilized by boiling for five minutes in a hopper devoted to them.

Bath water is also boiled for five minutes.

Sputum cups, compresses, and mouth swabs are put into paper bags, marked "typhoid," and burned in the boiler house furnace.

Bed and *body linen* are put into a special bag, marked "typhoid," and boiled in the laundry separate from other linen.

The *mattress* is sprinkled with a 2 per cent solution of formalin, marked "typhoid," also with date and ward, and sent to the fumigating room, where it is exposed to formaldehyd gas for twenty-four hours. Each mattress receives at least two fumigations, sometimes more, according to the demand.

Rubber sheet, rubber pillow case, bedstead, and *stand* are washed with soap and water and then with a 1:3,000 solution of corrosive sublimate.

Special *thermometers* are used for typhoid patients. After use they are washed with soap and water and kept in a 1:1,000 solution of corrosive sublimate.

Special *enema syringes* and *rectal tubes* for typhoid patients are washed in cold water, then in hot water, boiled three minutes, and kept in salt solution.

Special *dishes, cups,* etc., for typhoid patients are washed separate from other dishes in a special dish pan, placed in a dish sterilizer, and boiled for ten minutes.

Nurses wear *aprons* with long sleeves when making the bed, feeding, and bathing the patient. *Rubber gloves* are worn when the bed-pan is handled and when the mouth is swabbed.

The *clothes* worn by the patient on entrance are exposed to formaldehyd gas for twenty-four hours.

Of course, such measures as are above detailed can be carried out only in large institutions. Equally good results can, however, be obtained anywhere by the intelligent adaptation of means to ends. The Massachusetts State Board of Health officially recommends the following treatment of stools and urine:

"Milk of lime (one part freshly slaked lime to eight parts of water), or chlorinated lime (6 per cent), or carbolic acid (5 per cent), or formalin (10 per cent), or boiling in soda solution. The discharges should be received in a vessel containing some of the germicidal solution, and more should be added so as to cover the mass and be equal to at least twice the volume of the material to be disinfected. The entire contents of the vessel should then be thoroughly stirred, special care being taken to disintegrate lumps. The vessel should be covered and allowed to stand not less than one hour before the contents are discarded."

Compresses and all small articles contaminated, or specially liable to become so, should be burned.

Privies should be screened, water-tight, and cleaned only under official supervision.

Bed and *body linen* should be soaked in 5 per cent carbolic solution for several hours, boiled, or both. Bath water should be boiled.

When the surroundings permit, the stools and urine can be buried after disinfection, of course with due regard to wells or other water supply.

If the family is engaged in the milk or any other business connected with foodstuffs obvious special precautions are in order, and it may be necessary, in the interest of public health, to suspend such business until all danger of contamination is past. Four negative and consecutive examinations of the stools and urine should be required of persons thus employed before they are allowed to resume ordinary work.

The precautions which are so easy in large hospitals are often very difficult in the private house. Experience has indicated that it is necessary to explain in great detail from a bacteriological point of view the dangers arising from the care of typhoid fever patients. . To these explanations routine regulations can be added, with the expectancy that no slips in sanitary technic will occur. Without such an explanation it is often perfectly extraordinary how futile routine regulations are.

Carriers.—A chronic carrier should be kept under the supervision of the local board of health and not allowed to handle foodstuffs for others. If he moves to another place, the local health authorities of that place should be notified, if possible. It is, of course, obvious that such a person may start an epidemic running into the hundreds of cases. In this connection it is of interest to note the statement that, on December 3, 1911, Mary Wallon, otherwise known as "Typhoid Mary," entered suit against the city of New York for alleged false imprisonment by the Board of Health.

TREATMENT

Frederick C. Shattuck

Revised by Roger I. Lee

There is no specific therapy of typhoid fever. Much experimental work has been done in the use of various specific products of the typhoid bacillus in the treatment of the disease. While there have been a certain number of favorable reports concerning the use of some of these products, as yet these reports require confirmation, and, looked at broadly, one does not discover at this time any specific therapeutic agent in typhoid fever which holds very great promise.

General Care.—In any case in which typhoid fever is suspected—and it should be suspected in every continued fever until proved absent—the patient should be put to bed and treated provisionally as if he had typhoid. Even if the disease be mild, each case is a potential source of disease to others. In a case which is mild at first gravity may appear later, either from severe toxemia or one or more of the many accidents and complications incident to the disease. It is, therefore, of moment to save the strength from the start. We have all seen cases in which, from avoidable or unavoidable delay in diagnosis, patients have dragged themselves about and become so exhausted that this very exhaustion seemed a leading feature of their disease, perhaps the determinant one as to recovery. The slow development and long duration of typhoid afford a sharp contrast between this infection and some other acute infections, pneumonia, for instance, a point worthy of therapeutic consideration.

Should proper care be difficult or impossible at home, entrance to a hospital, if such be accessible, is to be urged. It is of the last importance to provide for proper nursing. If possible, there should be two nurses. If the eight-hour limit is adopted, either through unions or by law, at least three will be required. In severe cases three are none too many, some items of care—bathing, for instance—being difficult to carry out by a single nurse. Of course financial and other considerations only too often make the ideal unattainable. We must content ourselves with coming as near it as we can. The best room in the house, if possible with a sunny exposure, windows on at least two sides, an open fireplace, and convenient bathroom, is to be devoted to the patient. As in other infectious diseases, or, indeed, for that matter, in disease in general, the fewer unnecessary articles in the room the better. Of course carpets, curtains, and the thousand and one things with which the rooms of the well-to-do are nowadays encumbered are less objectionable in typhoid than in the eruptive infections; but they greatly and needlessly add to the burden of care of the room and interfere with the quiet so desirable about the sick.

Among the requirements of the sick room I give the open fire a high place. It warms rather than heats the room, and, above all, promotes ventilation. I do not think that the advantages of a combination of open fire and open window are as widely appreciated as they should be. Hard, thoroughly dry, non-snapping wood with a plentiful bed of ashes yields the best results to those who know how to secure them. It is easy to change, almost in a moment, from a brisk to as slow a fire as you please, or vice versa. Soft coal comes next. Anthracite is a bad third. The gas fire has its convenience. Direct radiation as a means of warming rooms is cheap and nasty.

Compresses and small articles are readily burned in the opened fire, if such there be. It is to be remembered that the disease may be carried from one patient to another or to a healthy person by an enema syringe or a thermometer. The risk of transmission through spoons and other feeding vessels is very slight with ordinary care.

The use of the bed-pan is to be rigidly enforced, as a rule. Few people take kindly to the bed-pan at first; but the habit is generally soon acquired, and a little water thrown into the rectum helps much to overcome the disadvantage and novelty of the supine position. Now and then, however, we have to deal with a patient who does not seem able to reconcile himself to the bed-pan. Its use involves more fatigue than does that of the cabinet at the bedside with proper assistance. If the net result of the bed-pan is squandering strength, a means less open to that objection is to be preferred. Common sense should rule here, as elsewhere.

The minimum output of strength is the underlying principle of the bed-pan. It is not likely that the sitting posture in itself can cause hemorrhage or perforation, and the chance that unjust blame may be attached to the attendant for a really unpreventable accident should not be paramount to the interests of the patient. The notions of the laity about matters medical have nearly always been derived from the profession, but are apt to be more or less out of date. The head of the procession precedes the tail. This seems all very trite, but is not so much so as it seems. We are all of us prone to follow rules—the line of least resistance. This is as good a place as any to insist on the application of active common sense to the principles of management of a person sick with a disease which we do not as yet know how to cure.[4]

The danger of leaving a typhoid patient alone, even for a moment and even when not seemingly delirious, must be mentioned and realized. A chance to jump out of the window, to conceal or use a razor, scissors, or the like, may be cunningly watched for and promptly seized by a mind which appears saner than it is.

The mouth, teeth, and tongue are to be carefully cleansed with a cotton swab and boric acid, or other similar solution, at least three times a day, and a little glycerin may be used on the lips. Sordes, and a dry, leathery tongue, like that of a parrot, are mute accusations of the doctor and nurse, as a rule. For many years all my typhoid patients have had their throats sprayed thrice daily with Dobell's solution, and I am confident that middle-ear inflammation has been decidedly less frequent under this routine.[5]

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[4] Very sick patients who cannot use a bed-pan may be allowed to defecate on a large pad which is subsequently burned.—Editor.

It has been said that the best treatment for bed sores is to discharge the head nurse. Certain it is that, under proper care of the nates and parts specially exposed to soil and pressure, bed sores are rare. Cleanliness and dryness are potent preventives. So also is change of position, and thus of the seat of pressure. The least sign of redness should lead to extra vigilance and the use of pure alcohol frequently over threatened areas. The air or the water bed, if available, may be a help. Rings can be made, in sizes to suit, of toweling or tow, and covered with cotton bandaging over a layer of sheet cotton batting. They have an advantage over rubber rings in that they are more absorbent.

Visitors should be excluded and interviews with members of the family brief. The mere presence of a judicious member of the family in the room, to spare the nurse or for other reason, may be not only admissible, but desirable. Only in the mildest cases should the patient be allowed to read. Reading aloud to the patient may be soothing, help to pass the time, and serve to divert the thoughts from business or other undesirable channels.

The covering of the patient should not include a bed-spread, especially if starched. Bed-spreads may gratify the eye of the careful housekeeper, but serve no really utilitarian purpose. If the size of the sick room and circumstances permit, two beds are better than one, each to be occupied twelve hours. The patient can easily be rolled from one to the other, gets refreshment from the change, and the mattress retains its shape better. Beds in private houses are apt to be too low for nurses to do their best work. A low, double bed and a heavy patient make a difficult combination. The prompt purchase or hiring of a hospital bed or a bed of that type will easily be economy in the long run.

Diet.—Typhoid fever is an acute infection varying in duration from three weeks to three months, if there are repeated relapses. After severe cases, or in those past the prime of life, in whom repair is relatively slow, convalescence is apt to be tedious. The most frequent cause of death is asthenia, the heart giving out owing to the action of toxins on the myocardium and on the central nervous system. Supportive treatment and the maintenance of the strength are, therefore, matters of great moment, far more so than in an infection of short course, like pneumonia. In tuberculosis, usually a chronic infection, we strive to increase the digestive limit and to feed the patient thereto. Although typhoid is a self-limited disease to a degree and in a sense that tuberculosis is not, I believe that the same principles as to diet should obtain in both diseases, were it not for one, and a vital, difference—the constant intestinal lesions of typhoid. There is no parallelism between the symptoms and the number, extent, or depth of the intestinal ulcerations. Loss of blood from an ulcer may at any time convert a mild into a very serious case, perhaps kill the patient directly, more often seriously add to the asthenia. Perforative peritonitis, general or local, the gravest accident in typhoid, is liable to occur even in the earliest part of convalescence. We have, therefore, to strike a balance between the needs of the body as a whole and the special care demanded by the ulceration and its seat. To limit the extent and promote the healing of ulceration which we can see, we do not set our ingenuity to work to devise an approach to the constant unrest of peristalsis, nor do we use fecal matter as a dressing. It is true that cow dung has been used for making poultices and may possibly be still so used in some bucolic districts. But its use for the purpose is not making headway, to say the least, and I do not know that it was applied to raw surfaces. As a matter of fact, typhoid intestinal ulcerations do heal perfectly in the great majority of cases, perforation and hemorrhage combined being responsible for probably not more than 1/10 per cent of the general mortality of 8 or 10 per cent. It seems, however, rational to suppose that a dignified and gentle peristalsis, and, as far as may be secured, unirritating intestinal contents, tend to reduce to a minimum the risks of these accidents which are still bound to occur sometimes, in spite of what we can do or what we can refrain from doing.

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[5] Even more important is the prevention of parotitis which was a frequent complication before the days of proper mouth technic.—Editor.

I was taught that milk should be the main or exclusive article of diet in typhoid fever, and for two weeks after the temperature had struck normal. This teaching I followed for some years after I came into the charge of hospital wards. At first, during the typhoid season, I hardened my heart against the prayers, even against the tears, of patients clamorous for articles of food which I now believe to be innocent. Two or three cases of continued fever, as the cause of which I thought myself justified in excluding typhoid, were fed on extra diet—whatever they wanted and the hospital could afford. They recovered safely, quickly enough, and comfortably. Subsequent review of these cases convinced me that I had been at first mistaken in diagnosis, that they had really gone through typhoid fever and had come out of it in better condition than was common in the Massachusetts General Hospital in those days. This set me thinking—very hard work for me—and led me to formulate a principle, adherence to which for twenty years has never caused me regret; on the contrary, only satisfaction. This principle is that every patient with typhoid fever should be fed with reference to his digestive power, with exclusion of such articles as in themselves or in their residue may be irritating to the raw surface in the gut or may produce undue peristalsis.

We have not escaped entirely from the old doctrine of inflammation and its starvation. We are inclined to fear the local manifestations more than the general disease, to treat the disease rather than the patient, sometimes to forget that a routine is our servant, not our master.

Those patients whose irritable stomachs led to the use of the term "gastric fever" must be fed with the greatest care on bland liquids, perhaps in very small quantities and at very frequent intervals. In my experience such gastric irritability is usually a relatively early and transitory symptom. Other patients seem ready to take and digest anything that we give them, even during pronounced fever. Between the two we see every possible gradation, as well as wide differences between the digestive power of the same patient at different periods in the disease. Food should be given every two or three hours. The interval should seldom be longer than three hours during the day, but may be exceeded during the night rather than wake the patient from a relatively natural sleep. Toxic stupor is not a valid cause for a longer interval. I still give milk, more or less, or none, according to the condition of the patient at the time. Since we have been encouraged to think in calories, we are told that a larger amount of milk is needed to maintain the body weight than can practically be given to a sick person. Even if this be true, a moderate loss of weight does no harm and is rapidly made good during the leisure of convalescence. Moreover, whether from ignorance, prejudice, or both, I confess to some skepticism as to the methodical application of caloric values to a living organism, as if it were a machine made in Germany. The living body has a surprising power of adaptability. We see individuals, as well as races, developing more energy than the caloric value of their food would seem to warrant. We must always remember that the living body is a variable and that the result of its multiplication by a fixed factor, assuming the calorie to be fixed, is liable to be a variable. But we cannot safely assume the calorie of daily life to be a fixed factor. All oatmeals are not the same, and in like manner there is a variation, which may be important, in every other article entering into the dietary of man. And, moreover, how about the cook? One cook surely differeth from another in glory, and those who are capable of large destruction of whatever caloric value a raw material of diet may contain are, unhappily, the rule rather than the exception.

Alexander Lambert now forbids milk altogether to his typhoid patients, and notices a greatly lessened frequency of meteorism since his interdict. On the liberal and mixed diet which I use meteorism is rare save in severe cases, and then seems attributable far more to toxic paralysis of the gut than to dietary influence.

Warren Coleman has made careful studies of the application of caloric values to the feeding of typhoid patients, and finds that by the addition of cream and of sugar of milk to milk he can prevent body waste. A patient weighing 150 pounds should be given the food equivalent of 4,000 calories a day. His daily diet is something as follows:

1½ quarts of milk.
1 to 2 pints of cream, 25 to 30 per cent fat.
½ to 1⅔ pounds of milk sugar.
3 to 6 eggs.
Stale bread or toast with butter.

This study is of interest, and may be of importance in cases presenting unusual difficulties for proper nutrition; but it seems to me in the great majority of cases caloric values can be disregarded. If the patient is comfortable, progressing favorably, without indication of digestive disturbance, and is fed up or nearly up to his digestive limit, it does not make any difference how many calories the food contains.

Coleman's further experience of a high calorie diet in typhoid fever has been very satisfactory. Those who have tried to adopt Coleman's method of feeding, particularly in a private house, become painfully aware of the manifold difficulties. Coleman himself emphasizes certain salient facts:

1. Typhoid fever does not alter the patient's preferences for food, or remove existing food idiosyncrasies.
2. The diet must be made to fit the patient, and not the patient the diet.

In addition to any theoretical considerations as to caloric requirements, the main factor must always be the ability of the patient to take care of the food, and the amount and kind of food must in the last analysis be solely determined by its clinical effect upon the patient. Sick patients will obviously take less food, and must be given food in liquid or semisolid form, or at least in some form which does not require mastication. While very few physicians have been able to repeat in private practice Coleman's experience, very largely due to the fact that a physician does not have available trained personnel with adequate experience to carry out his suggestions, nevertheless, the passage of time has indicated that liberal alimentation in typhoid fever is accompanied by many beneficial effects, and apparently by no deleterious effects.

The arguments in favor of the dietetic principle above stated are enhanced comfort to the patient and a shorter convalescence. Incidentally, loss of hair as a sequel of the disease, I suppose an index of markedly lowered nutrition, practically has not occurred since I abandoned exclusive milk diet, though it was not uncommon before. I have been accused of giving pork and beans to my typhoid cases, partly, doubtless, but not wholly, in fun. The following list of admissible articles and preparations claims to be suggestive rather than exhaustive:

All liquids, including broths and cocoa.
Soups—purée of oyster, clam, potato, etc., etc., carefully strained.

Gruels, strained if containing rough particles.
Ice cream, blancmange, junket, milk toast without crust, sherbet.
Eggs, raw, soft, boiled, lightly scrambled.
Meat, finely minced, scraped raw beef.
The soft part of raw oysters, macaroni, rice.
Orange and grape-fruit juice.
The soft part of baked or stewed apples.

The best results will be obtained only by the physician who applies sound principles to the management of his case, allows no change in conditions to escape him, and is ever ready to modify details as the idiosyncrasies of the patient or the varying features of the individual patient demand. Water should be given freely, if for no other reason, with the hope of causing large renal output and thus elimination of toxins soluble therein. I have seldom given water in the quantities advocated and administered by the late Dr. E. W. Cushing, of Cleveland, one to two gallons a day. This has been aptly termed "a species of internal hydrotherapy."

The best criterion for a desirable amount of water would seem to be the chart of the daily urinary output. The output of urine in typhoid fever should be 1,500 c.c. (50 ounces), and the fluid intake should be sufficient to keep the urinary output at that level. There is no evidence that any benefit attaches to the further forcing of fluids, and there is much to be said in favor of a steady fluid intake as opposed to the high waves created by some enthusiastic nurse.

I am inclined to believe it possible to enhance the danger of cardiac dilatation through the extra demand made upon a weak heart in taking care of large amounts of fluid. If for any reason water enough cannot be given by the stomach, it should be given by the rectum, that is, normal saline solution either in bulk or by seepage, as may seem wise. If the rectum be rebellious, it may be desirable to employ hypodermoclysis. Glucose 10 per cent, lactose 6 to 8 per cent can, if it seems desirable, be added to the water, introduced either into the rectum or under the skin.

The amount of actual food in terms of food value which can be administered by rectum is on the whole rather slight. It is probably advisable to utilize the rectum entirely for the administration of fluid without running the risk of creating an irritability by the addition of food of low caloric value. The administration of fluid intravenously has been shown to be of very temporary benefit. It may be of value in a temporary crisis, but it is not a satisfactory method of supplying fluid to the organism. There are indications that the intravenous route may in the future be utilized for the supply of calorific foods, but as yet no considerable alimentation is possible in this fashion.

It is held by some that alcohol is always and everywhere noxious; but it is generally admitted that it is a food, and as such is touched upon here.

It is not only capable of directly producing energy, but also, probably in some way not fully understood, guards the tissues against waste, especially when a severe infection has taken possession of the body. Many, perhaps the majority, of cases, require no alcohol from start to finish. If the pulse is good and assimilation and secretion satisfactory, there is possibly even less reason for giving alcohol than to a person in full health; but if the heart shows distinct signs of undue weakness, if hypostasis is threatening or marked, if the power to take, retain, or appropriate nourishment is unduly lowered, I believe it to be a grave error in judgment to withhold alcohol. It can be given as absolute alcohol diluted with water, nearly tasteless, or in the form of liquor, wine or beer, as may seem or prove to be wise. Whatever form of alcohol be chosen, it is better to give it pure or with water alone, and not mix it with articles more commonly classed as food. The danger of forming an alcoholic habit is practically *nil* in the subjects of acute general infection. They are more likely to acquire a distaste than a liking for it. The presence of the smell of alcohol on the breath may be deemed evidence that the dose already given has not been used up, and thus an indication to wait and perhaps to reduce the next dose. An intelligent and reliable nurse can be of great service in helping to decide when and how much alcohol to give. Three or four ounces of whisky or its equivalent rarely needs to be exceeded during twenty-four hours; but cases now and then are met in which it should be given, usually to tide over an emergency, up to the limit of toleration. It can, of course, be added to enemata, or even put into a glucose-salt-solution and introduced under the skin in the strength of an ounce to the pint.

Doctor Shattuck has outlined with convincing tolerance the brief of the use of alcohol in typhoid fever. It is now generally accepted, I think, that alcohol is only used as a food when there is an insufficient supply of available carbohydrate or fat. That condition frequently obtains in typhoid fever. It has not been my personal experience that alcohol is a stimulant in typhoid fever or in any other acute infection. It is true, however, that the physiological effect of alcohol is to give a fictitious sense of well-being and in consequence of that fictitious sense of well-being the patient may well forget his ache in his bones, the headache, and all the petty annoyances of his disease. There are obvious indications for the use of alcohol in typhoid fever, rarely as food, but not infrequently for its most important physiological effect.

If the patient has been liberally fed during the fever no great change is in order for convalescence. I do not nowadays often see the ravenous appetite or the rapid digestion, leading one to compare the stomach to a dredge at work, so common during the restricted diet period. It is to be remembered that the subsidence of fever does not mark the healing of the ulcers, which may be delayed several weeks. As before stated, we have no means of even guessing how deep and extensive or numerous these may be. Those of us who are past middle life recall how generally relapse was attributed to a dietary error, and the cross-examination of the nurse or patient which was held to find out whether a friend, soft alike in heart and head, had brought forbidden fruit.

We now know that true relapse, a fresh infection from failure to secure immunity, cannot be so produced. An error in diet may cause hemorrhage or perforation; it may result in transient elevation of the temperature for a few days perhaps. That it can start up a relapse is not credible. It may be stated that fever recrudesces; typhoid fever relapses. It may be well for the physician who feeds his typhoid cases more liberally than his neighbors to explain this matter to the family at the outset, and thus to forestall criticism.

Hydrotherapy.—In modern times Currie, 1787, was the first to employ and advocate cold water externally in typhoid fever and in other general infections. Nathan Smith began to employ it in 1798 in this country, but did not publish his cases. It was a bold thing to do at that time, and the voice of Currie was as that "of one crying in the wilderness." The practice ran too counter to the notions and prejudices of the times. It was revived in 1861 by Brand of Stettin, whose experience was so large and results so good as to compel attention. His following was at first larger in Germany than elsewhere, and, a curious fact, earlier on a large scale in Australia (Hare of Brisbane) than in England. France, after the Franco-Prussian War, was not prejudiced in favor of things Germanic. The English are conservative; and the expense involved in the large increase in attendance demanded by tubbing counteracted, in this country of high wages, our readiness to try any and every new method of treatment, sometimes, alas! even if not well based or reasonable.

It seems a fair statement that Brand's method, with or without modification, was helped in its adoption by the opinion widely held about that time of the danger of high fever in itself. The cloudy swelling of the parenchymatous organs was laid at the door of the fever, reduction of which tended toward conservation, to use a word which is now so much in vogue. The temperature was not only an index for the use of the cold bath, but also of its efficacy. We know that fever is a concomitant of acute general infections, and some question whether, in its usual limits, it may not be a part of the means employed by the organism to fight the invading enemy. We are, therefore, loath to-day to combat fever as such, save when it takes the form of what is called hyperpyrexia in which the very temperature is dangerous, as in thermic fever and in the rare cases of infectious disease in which all balance between heat production and heat dissipation seems to be temporarily lost. The introduction of the coal-tar antipyretics was hailed with enthusiasm and joy by the thoughtless, with interest by all. Their effect in reducing temperature markedly and promptly was clear. Might they not save us the toil and expense of the Brand method? It did not take very long to answer this question in the negative. As routine agents they were soon found to endanger the life of the patient, even those of them which are least depressant to the heart and guarded by caffein at that. They still have a limited application in typhoid, to be mentioned later.

It cannot be too clearly borne in mind that the purpose of hydrotherapy is not primarily to reduce temperature. Its purpose is to promote deep breathing, thus aiding the respiratory and circulatory functions; to exert a beneficial influence—stimulation?—upon the central nervous system; to lessen delirium—toxemia of the cerebral cortex; to diminish restlessness and promote natural sleep; in short, bring about a more normal state of the whole organism. This is often noted after hydrotherapy even when the water has not appreciably lowered the temperature; nay, even when the temperature rises after the bath. The thermometric reading still remains the routine index for the use of the bath. The true index is, of course, the balanced estimate of the state of each patient at the moment. The experience, insight, and judgment which lead to right decision can neither be directly imparted by teaching nor set down in writing. The thermometric index is, when checked by fairly simple, if not obvious, reservations, pretty safe, especially if the nurse be competent. It is, at all events, the best single index we have at present.

I believe it a fair statement that the use of cold water as laid down by Brand is losing rather than gaining favor, at least in the United States. It is felt that equally good results are obtainable by forms of hydrotherapy which are less perturbing to the patient as well as to domestic life, and which require for their carrying out an amount of attendance more nearly at the command of the average family or hospital. In the Massachusetts General Hospital we have never adopted the Brand method in full. In the height of the season I have repeatedly known 50 per cent of the medical cases to be of typhoid fever. Proper tubbing of any such number of cases involves no small addition to the thirty-six dollars per week which it now costs to keep a patient, not counting the interest on the plant. That Brand and his followers have done yeoman service in bettering the treatment of typhoid fever cannot be disputed, even by those who are not in full communion in all details.

In essentials the Brand method is as follows: When the three-hourly rectal temperature reaches 102, a bath in a tub by the bedside is in order, the water from 65° to 70° F. The bath is preceded by alcohol in some form, and a sponging of the head and chest with cold water. While in the bath, constant and vigorous friction is used on the limbs and chest, not on the abdomen, and a cool compress is kept on the head. The duration of the bath is from ten to twenty minutes. The patient is then dried, preferably on a blanket to be removed later, and given some nourishment. To some persons the procedure is very obnoxious, so much so as not to warrant its continuance. Others find it very grateful, especially after they note that a secondary betterment follows. The shivering and cyanosis which sometimes occur are far from being as indicative of harm or danger as any one seeing them for the first time would naturally deem them. In the Johns Hopkins Hospital canvas strips are so attached to clamps on the side of the tub that the proper degree of immersion of the patient resting upon them can be readily secured. The routine bath temperature is 102½, and the water varies from 85° to 70°, the higher figures being used for the first few baths, for the very young, for the old, or for other special reason.

The modifications of this method are many, the main underlying motive for such modification being economic. The bed can be made to serve as a fairly good tub by a large rubber sheet converted into a trough by blanket rollers under the sides and ends. Water at the desired temperature is easily introduced, and can readily be taken out with a sponge. Some bits of ice serve to maintain the water temperature, which would otherwise be raised by the warmth of the body and of the bedclothes. It is easier to rub the patient in a high bed while the bathing is going on than it is in a tub which involves stooping over; and, moreover, all lifting is saved. This plan has been long in vogue in the Massachusetts General Hospital and seems to give good results.

Liebermeister thought the cold wet pack quite as good as tubbing. The patient is wrapped in a sheet wrung out of cold or even ice water, covered with blankets, and rubbed. The sheet should be changed every ten minutes and thrice applied. The warm pack is applied in the same way, water at a higher temperature being used. Rubbing need not be so vigorous nor change of sheet so frequent with the warm pack. This form of hydrotherapy is applicable to those who from age or other cause are not fit subjects for cold water.

The fan bath consists in promoting evaporation from a sheet covering the patient sprinkled with ice-cold water from a garden sprinkler, while the limbs and chest are rubbed as in the Brand method. Nathan Smith speaks of fanning with a sheet. Other modifications are the warm bath, either kept warm or gradually reduced in temperature by the addition of cold water or ice; and, again, simple sponging. The latter is varied in many ways as regards the temperature of the water used, the addition of alcohol up to 50 per cent or more, and the amount of body surface exposed and sponged at a time. However askance these spongings may be looked upon by the strict followers of Brand, they have seemed to me all-sufficient in many cases.

Indeed, hydrotherapy in typhoid fever, as all therapeutic measures wherever applied, must be mother-tinctured with common sense. Unless the nurse be very experienced and reliable the first bath or two should be watched by the physician in private practice, by a house officer in a hospital. The form of hydrotherapy, its duration, repetition, and temperature should be suited to the individual patient at the time, with due consideration of the after-effects upon him even more than on his temperature. Those with a thick fat layer stand lower water temperatures than do the thin. Osler gives the mortality at the Royal Victoria Hospital, Montreal, for six years, 5.4 per cent; at the Johns Hopkins, 9.1 per cent in 1,500 cases. At the Massachusetts General Hospital, where we have never applied the Brand method in full, the mortality of 2,651 cases is a shade over 10 per cent.

One fact leaps in the faces of those of us whose professional experience goes back forty years or so. The cases of which the term "typhoid" is really descriptive are far fewer than they were formerly; are, indeed, the exception; and I do not find it easy to demonstrate to my students to-day the "typhoid state," so-called. This change I believe to be due in the main to the vast improvement in nursing which has taken place since my student and early professional life, and to more rational feeding. Under the head of nursing, I should include so much hydrotherapy as thorough cleanliness demands. Whether epidemics are milder to-day than they were formerly, as has been claimed, I do not know.

The comparative rarity of typhoid fever in the present day has done much to discourage the use of hydrotherapy as it was employed twenty years ago. A recent inquiry showed that neither medical students nor nurses were familiar with the Brand bath. Most cases of typhoid fever are nowadays given some form of sponge bath or alcohol rub. It is certainly the part of wisdom to apply a procedure which is familiar, rather than to embark on unaccustomed therapeutic agents. Most of us who were familiar with typhoid fever when it was very common are still convinced that there is the very toxic case of typhoid fever in which the Brand bath gives very remarkable results, and which is not at all affected by milder hydrotherapeutic methods. For the most part, however, the patient with typhoid fever can be kept comfortable with sponge baths and alcohol rubs.

Hemorrhage.—It is assumed that the nurse is alive to the importance of watching for signs of blood. If this appears my practice has been to limit peristalsis as far as may be by withholding nourishment, if the patient's condition warrants it, for a day or two; or by restriction of the diet in quantity and a change in quality to broths, milk, and water. Morphia is also to be used, preferably under the skin, at first 1/4 gr. for an adult, and then 1/12 to 1/6 every three to six hours, as may seem wise. Moderate narcotism is not objectionable. The respiration affords a better indication of the limit of tolerance than the pupils. A respiratory rate of 12 to the minute is perfectly safe. The behavior of the pulse and temperature is, of course, a far more trustworthy index of the amount of blood poured from the vessels, and of the effect of this loss, than is the amount passing the anus. Ice-bags to the abdomen are almost universally advised. I do not forbid them, but very rarely have ordered them. Baths should be stopped, the utmost quietude secured, and the foot of the bed raised if the effects of blood loss are evident. In cases of moderate hemorrhage, especially if single and not too soon repeated, starvation and morphia for perhaps thirty-six to forty-eight hours suffice. It may become a nice question whether or not to use salt solution under the skin or intravenously, or to have transfusion done. Enemata of salt solution are provocative of peristalsis, an objection to which seepage is, however, less open. We must try to strike a balance between the danger of death from the loss of blood, which has already occurred, and from that of provoking fresh bleeding inherent in the measures calculated to obviate the first danger.

Typhoid hemorrhage in general presents the same problems as do other hemorrhages. Most cases of typhoid hemorrhage will take care of themselves, without further treatment than rest. The loss of fluid must be compensated as early as possible. Consequently it is highly desirable to begin the administration of fluids in small amounts as early as it does not interfere with rest.

As in the case of hemorrhage elsewhere the best indicator of the severity of the hemorrhage, and therefore the guide to treatment, is the chart of the blood-pressure. The amount of hemoglobin is notoriously a poor indicator of hemorrhage because the percentage of hemoglobin only falls when the remaining blood is being diluted by tissue fluids (which is a satisfactory condition, as it represents a natural attempt of restoration of blood volume). At once when a hemorrhage is either apparent or suspected, blood-pressure and pulse charts should be inaugurated, and the decision to transfuse or not to transfuse should be made on the general conditions of the patient and on the course of the pulse and of the blood-pressure. A blood-pressure below 90 is not necessarily serious, but a falling blood-pressure going below 90 is an indication for transfusion in the presence of known hemorrhage. The transfusion should be at least 500 c.c. of compatible blood, and may be carried out by any of the standard methods. I have no personal preference between the multiple syringe method, the sodium citrate method, and the paraffined vessel method. There has been much alarm on the ground that a transfusion might start up again an arrested hemorrhage. On the whole, experience does not seem to confirm this apprehension. In any event, it is the part of wisdom not to delay transfusion too long. There are probably two types of hemorrhage: one the actual rupture of a vessel, which is a purely mechanical hemorrhage; the other, perhaps somewhat mechanical in nature, but largely due to the prolonged coagulation time of the blood. In typhoid fever, as in most acute infections, the coagulation time of the blood is considerably prolonged in the febrile stage. Observations on the clotting time of the blood are often of great interest but do not alter the general indications for the treatment of typhoid hemorrhage. Certainly transfusion is the most effective remedy for delayed coagulation time of the blood. Some observers report excellent results from the use of calcium, usually in the form of calcium lactate in daily doses of 1 to 4 gm. (15 to 60 gr.). Adrenalin, in doses of 1 to 1.5 c.c. of a 1:1,000 solution, used hypodermically or with salt solution by hypodermoclysis, has its enthusiastic advocates. A customary procedure is the application of the ice-bag to the abdomen, which certainly does no harm, although there is very little evidence of its being of value.

The cases in which surgical treatment is to be invoked must be very, very rare. The situation is quite different from perforation. Most cases of hemorrhage recover if let alone. Nearly all cases of perforation die if let alone. A patient with hemorrhage whose bleeding is to be stopped only by operation is pretty sure to be killed by the operation. We see patients recover from seemingly desperate conditions who could, humanly speaking, not have recovered had the shock of operation been superadded. At least five days should elapse between any evidence of blood loss and the resumption of baths and normal diet. In every case of typhoid fever in private practice, sterile, normal salt solution and the means for its introduction should be on hand in the house as soon as the diagnosis is reached.

A brief statement of a personal case is here appended, illustrating well intestinal hemorrhage, obstinate vomiting, and insomnia, and their treatment:

A young man of 26 passed through the primary attack of typhoid uneventfully, as also the first two weeks of an intercurrent relapse. Nausea then became troublesome, and some food was given by the bowel. November 7, 2 ounces of clots at 9 : 30, 15 ounces at 11 : 30 A. M.; patient blanched, very weak. Soon after the stomach absolutely refused food. November 8, pulse barely perceptible. Salt solution intravenously at 9:30 A. M. with marked and immediate increase in the volume and the strength of the pulse. Vomiting and nausea controlled by morphia hypodermically. That evening brandy and shaved ice, a dram (4.0) every two hours, was retained; strychnia, gr. 1/30 (0.002), was given every two hours hypodermically; nutrient enemata every six hours. November 10, pulse 160, fair quality, condition very weak, extremely restless, sleepless, exhausted, delirious at times, involuntary stools. A hypodermic of 1/200 gr. (0.0003) hyoscin hydrobromate was followed by peaceful and prompt sleep, after which recovery was uneventful.

Perforation.—It is to be remembered that in a toxic patient the usual signs of perforation may be more or less blurred or even absent. It is of the last importance that the nurse be conversant with the symptoms and signs suggestive of perforation, constantly on the watch for their advent, and prompt in notifying the attendant. The earlier operation can be performed the better the chance of saving life, unless profound shock may counsel delay. If the patient be in fairly good condition it is probably safer to explore unnecessarily than to lose precious time with the perforation. The possibility that perforation may result in a local peritonitis only, which can later be opened or may discharge through the bowel or elsewhere, is not to be counted upon. The statistics of laparotomy for typhoid perforation are steadily improving with prompt diagnosis, early operation, and the acquirement of the necessary skill by a larger number of the profession. In a recent hospital case the symptoms were so strongly suggestive of perforation that the belly was opened, but no perforation found.[6] Nobody would have suspected from the chart that any operation had been done, or, if informed that it had been done, been able to fix its date, and recovery was uneventful. Severe pain at the time of, or following, the perforation may warrant a hypodermic of morphia in spite of the mask which this drug is liable to throw over the symptoms. The promptness with which a decision as to operation and the performance thereof can be reached is a factor in the use or withholding of morphia. A hot flaxseed poultice, if the weight can be borne, or dry heat which can be maintained by a Japanese hand-stove, with which every house should be provided during health as a provision for illness, can do no harm and may notably alleviate pain.

Harte and Ashhurst collected and analyzed 362 cases of operation for typhoid perforation, with a mortality of 74.03 per cent. The following table shows the relative mortality in twelve-hour periods:

RELATIVE MORTALITY IN 12-HOUR PERIODS

Hours after Perforation	Total No. Cases	Per Cent Mortality
First 12	130	73.0
Second 12	84	73.8
Third 12	31	93.5
Over 36	55	67.2

It is reasonable to hope that the next statistics of operation for this purpose will show a lessening mortality.

It is impossible to furnish accurate comparable statistics in regard to the mortality after operation for perforation. It is obvious that perforation, while presumably nearly universally fatal if unoperated, is, nevertheless, only one of the conditions which the patient is combating.

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[6] It is quite certain that no clinician will save the maximum number of patients with perforation without performing some unnecessary operations.—Editor.

Increasing experience indicates that under hospital conditions exploratory laparotomy may be performed for suspected perforation with relatively little detriment to the patient. As a matter of fact, certain cases suspected of perforation and operated upon needlessly show a striking and prompt improvement dating from the operation. Operations are much more serious affairs for typhoid fever patients in the average home. It is reasonably certain that on the whole it is wiser to operate upon a few patients in whom perforation does not exist, than to permit to die unoperated a few patients in whom perforation does exist.

Circulation.—The principles underlying the treatment of circulatory disturbance and failure in typhoid fever are the same as in other specific fevers. The duration of the disease and its natural termination by lysis are factors of import. The failure of the heart is far more apt to be due to the poisoning of the nervous centers than to myocardial changes, a fact which goes far to explain the lack of success which too often attends our efforts. Unless the pulse exceeds 120 in rate, or the first sound is specially feeble, it is seldom desirable to employ alcohol or other so-called heart stimulants. My position with regard to alcohol has been stated under Food. A heart beating 120 per minute and showing a tendency to rise in rate will bear close watching and careful consideration at each visit. I have not found digitalis and its congeners often of value, save in as far as the giving out of the heart may be due to dilatation, that is, myocardial change. Digitalis is, I think, best given in tincture and injected deeply in a muscle; absorption is more sure as well as more rapid than from the stomach. Ten or 15 minims or more can be thus given twice a day. Experience confirms Doctor Shattuck's statement, which, put in another way, is that digitalis does not seem to be of any value in typhoid fever, except in those cases in which there is already existent damage to the cardiovascular system. In such cases digitalis may be employed with benefit from the beginning. The form of preparation of digitalis is of no particular importance, except in so far as it is necessary to use a preparation which has been tested and known to be physiologically potent. Powdered leaves of active digitalis in dosage of 1 to 9 gr. (0.065 to 0.6 gm.) daily, may be used by mouth. Digifolin in the same dosage may be used subcutaneously. If digitalis is to be used, the patient is preferably "digitalized" very promptly. The sodiobenzoate of caffein, 2 to 4 gr. (0.13 to 0.26) subcutaneously every four to six hours, has now largely supplanted strychnia in the Massachusetts General Hospital. Camphor, conveniently available in the form of camphorated oil, a 10 per cent solution, can also be injected under the skin and repeated as often as may seem desirable. Its effects are, of course, transitory. So also ether. Dry heat locally applied seems to be an efficient heart stimulant.

Ortner calls attention to phenomena which he attributes to diminished vasomotor tonus of toxic origin: namely, dicrotism and pseudocelerity of the pulse, pulsation of the smaller arteries, capillary pulse and centripetal venous pulse. Signs of increased cardiac activity, particularly a stronger apex impulse and increased aortic second sound, may indicate that the heart is not primarily at fault. In the circulatory collapse which may supervene salt solution under the skin or intravenously is called for and may be followed promptly by improvement.

Lungs.—Bronchitis, in greater or less degree so frequently a feature of typhoid fever, very seldom needs any drug treatment, as by expectorants or sedatives. Cyanosis is far more apt to depend on general toxemia and cardiac weakness therefrom than upon the mechanical interference with blood oxygenation caused by bronchial secretion. Hypostasis may often be prevented from passing into pneumonia by changing the patient's position every few hours from the back to one or the other side, and by treatment designed to support the heart. If pneumonia of any form supervenes, the windows should be more fully opened and no effort spared to keep the heart going. The occurrence of pneumonia in typhoid fever really alters the general treatment very little. The use of oxygen may be beneficial, as in the case of uncomplicated pneumonia, but, in order to secure good results, oxygen should be administered with a specially prepared mask. A very rapid respiration with relatively or sometimes perfectly clear lungs is, of course, toxemic and can be influenced, if at all, only by means calculated to counteract the toxemia. It is a rare feature and has not seemed to me of specially serious import.

Genito-urinary Tract.—Those rare cases in which the disease in its onset or early stage seems to vent itself on the kidneys especially, which can be mistaken for acute nephritis of other origin, and to which the Germans have applied the term "nephrotyphus," do well, as far as I have seen, the renal process soon subsiding. In such cases the diet should be that adapted to acutely disabled kidneys, and no bathing other than careful sponging under the bedclothes, or a hot, wet pack, is permissible. About the time of the Spanish War (1898), it became common knowledge that a pure culture of the typhoid bacillus may pass off in the urine. This does not seem to damage the kidneys or to do the patient any harm; but it is, without question, a means by which the disease has been much spread in the past, and the danger is more insidious even than that from the intestinal output, in that the inoffensiveness of urine makes people less careful where they deposit it and less scrupulous about washing their hands. Moreover, one urinates five or six times a day, but ordinarily one defecates only once. There is much and skilled labor involved in repeated examinations of the urine to find whether or not it contains typhoid bacilli and is thus specially dangerous.

In 1898 I began the routine treatment of giving every patient with typhoid hexamethylenamin, 7½ to 10 gr. (0.5 to 0.7) every eight hours for two successive days in each week from entrance to discharge. So prompt and so absolute are the effects of this agent on the Bacillus typhosus that I felt we could safely disregard frequent examination of the urine for that germ. For the past few years, in compliance with the request of the State Board of Health, which was carrying on some comparative studies, all my hospital patients have had the drug in the above doses thrice daily until discharge. The cases in which the use of the remedy, whether intermittent or persistent, has caused any untoward symptoms are very few, and these symptoms rapidly subside on stopping the drug. Hexamethylenamin, of course, is active only in an acid urine. If the urine is alkaline or neutral, acid sodium phosphate in doses of 10 gr. (0.65 gm.) or more may be administered thrice daily to change the reaction of the urine. It is probably undesirable to give this drug with hexamethylenamin on account of possible incompatability.

Gastric Irritability.—Gastric irritability, with or without vomiting, may be a more or less constant feature of the disease and give rise to the term, now happily nearly obsolete, "gastric fever." It is far more apt, however, if it occurs at all, to be temporary or initial, though it may appear at any period. If initial the symptom usually soon subsides under rest and light judicious feeding. It may, however, be well to give the stomach absolute rest for a day or more and resort to seepage, enemata, or salt solution under the skin, as may seem wise. The extragastric means of alimentation are apt to be more needed, and, if called for, to demand greater vigor in their application when obstinate vomiting occurs late in the disease which has sapped the strength and seriously drawn on the reserve supply of fat. If the character of the vomitus and other signs suggest that the vomiting is due in whole or in part to food retention in the stomach, the organ should be washed, sometimes a useful procedure in obstinate vomiting from any cause.

The drug treatment of the condition is quite subordinate to that sketched above, and differs in no essential from that applicable to the irritable stomach of any severe infection, which is far more likely to impair than to increase normal glandular secretion. Thus is explained the favorable effect of the mineral acids, especially of dilute HCl. Sometimes cocain in ¼ gr. (0.02) doses seems of service. Very rarely morphia, in hypodermic form, is called for, but is not to be given without serious consideration of all the features of the case and of any valid contra-indication to its use which may be present.

Management of the Bowels.—The demonstrated presence of typhoid bacilli in the blood in the earliest periods of the disease, even before fever appears, should give the death blow to efforts either to abort the disease or to modify its course by preliminary purges and so-called antiseptic treatment of the bowel. As far as my experience goes, more than half the cases have no diarrhea at any time, unless as a result of drugs. A dose of calomel can do no harm, especially if the bowels have not been fully opened, when the patient first comes under observation. It is to be always borne in mind that diarrhea, if present, is an expression of catarrh rather than of the ulcerative process. With a diet suited to the special case, and good nursing, troublesome diarrhea is rare. It is to be treated much like diarrhea arising under other circumstances: by a mild laxative if retention is believed to be a factor in its production; by diet, by bismuth, in doses seldom exceeding 20 gr. (1.3), preferably the subcarbonate; or such other astringents and correctives as may seem or prove to be advisable. If the discharges are very foul, betanaphthol may be added to the bismuth. Paregoric is sometimes useful. In the more obstinate cases one of the stronger opium preparations, as opium in powder or extract or tincture, may be called for. An irritable stomach may make it desirable to give the opium in a small enema with starch, or in suppository.

Meteorism is apt to be difficult to overcome. Save in exceptional cases, where it is due to faulty chemistry in the gut and passes off with rectification of the same, it is an expression of poisoned nerve centers and a paretic bowel. Of course, the prime object is to lessen or overcome the toxemia, as we try to overcome any septicopyemia, a difficult task at the best, sometimes quite beyond our power. Turpentine stupes and the rectal tube may be used. With turpentine internally in typhoid fever, save as an addition to an enema, I have no experience, and confess to being afraid of it.[7]

I know nothing comparable to an ounce or two of pure glycerin in the rectum as an aid to the expulsion of intestinal gas. If peristalsis can be instituted glycerin is pretty sure to do it; but the danger of thus causing perforation and hemorrhage has deterred me from its use in typhoid fever. Some surgeons are enamored of an enema of soapsuds with glycerin and Epsom salts. Thus diluted I believe the glycerin to be nearly inert. In cases requiring artificial aid to move the bowels the safest reliance is on enemata, which I am apt to use every other day. Some give them daily. It is very rare that a laxative by the mouth is called for during the height of the disease. As convalescence approaches or is entered on, the possibility that a continuance or recrudescence of fever may be due to fecal retention is to be kept in mind. I have repeatedly seen what I feared might be a relapse disappear after castor oil, calomel, or another mild laxative, and an enema, resulting in free evacuation. If a few ounces of olive oil, or what is commercially called such, can be retained in the bowel for some hours, it may help to clear the lower intestine by softening the fecal masses.

Certainly distention, a generation ago, was one of the most conspicuous features of typhoid fever. Since Doctor Shattuck had the courage to feed typhoid fever patients, and his methods have generally won acceptance, tremendous distention is certainly unusual. It may be safely said that nowadays distention requires no special treatment in the average run of cases. It is, I think, a safe principle to act upon that few cases of typhoid fever will require any other treatment for intestinal disturbances than slight modifications of diet and the routine enema which should be given every other day, or in some cases every day. It is probably wise, everything being equal, to insist upon the enema every other day, even in the presence of apparently satisfactory movements of the bowels or of diarrhea. Diarrhea may be entirely avoided by the proper administration of a cleansing enema. It should always be borne in mind that fecal impaction is not uncommon in typhoid fever, particularly in the period of convalescence, and particularly in cases cared for in their own homes. Rectal examination often gives information of very great value.

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[7] The addition of 1 or 2 drams of tincture of asafetida to the enema, while not pleasing to the family, may give relief to the patient.—Editor.

Incontinence of the bowels is, of course, a sign of great toxicity. It demands the best of care of good nurses. It is undesirable to leave patients on a bed-pan for long periods of time. Soft pads of oakum, tow, gauze, etc., are far preferable.

Insomnia.—Insomnia may be troublesome and require attention at any period in the disease. Notable cardiac weakness seems to me to contra-indicate the use of the coal-tar products, trional, veronal, sulfonal, sodium-veronal. Personally, I do not believe chloral to be the heart depressant it is credited with being by many. A bromid, chloral, or a combination of the two, often proves all that is necessary. If there be active delirium which is not quieted by bathing and ice to the head, opium in some form, preferably morphia under the skin, is called for and may be repeated, if it acts well, in such doses and as often as the features of the particular case may seem to demand. Sometimes hyoscin hydrobromate, 1/100 to 1/200 gr. (0.0015 to 0.0007), injected under the skin, acts better than anything else. On the other hand, I have known it to increase delirium. This seems to me largely a matter of idiosyncrasy, not determinable beforehand. The danger of intensifying the delirium has led me to limit the use of hyoscin to those cases in which morphin and other measures fail. Sometimes hyoscin and morphin combined act better than either alone. When combined, a rather smaller dose of each should be given than of either alone.

Headache.—This symptom is rarely prominent or troublesome except in the earlier stages of the disease and, therefore, before the heart has begun to weaken. Severe headache seems to me the only justification for the use of a coal-tar antipyretic in typhoid fever, and often one of this class of remedies proves serviceable for the purpose. No one of these preparations is safer than phenacetin, which should always be combined with caffein, 1 gr. (0.065) of the latter to 5 gr. (0.3) of the former. The first dose of phenacetin should never exceed 5 gr. (0.3), presence of fever from any cause seeming to diminish the tolerance of this class of remedies.

It is wiser not to repeat the dose in less than two hours. Repetition and the frequency thereof must be a matter of careful judgment. If neither relief nor untoward results follow, the dose may be increased, but very cautiously and under trained observation. Now and then this symptom can be relieved only by a hypodermic of morphia. The ice-cap may help.

Nosebleed.—Epistaxis rarely needs any treatment. I have once seen death occur from hemorrhage, uncontrolled or uncontrollable. Measures to stop excessive bleeding are essentially the same as for nosebleeds under other conditions: compression of the nasal arteries, ice to the nose, adrenalin locally, or plugging the nares. As a rule, epistaxis is an early symptom and occurs before pronounced weakness has developed. Whether and how much the patient is to be propped up in bed, as a means of stopping his nosebleed, depends on his general condition and the stage of his disease.

Parotitis.—This, though uncommon, is more likely to occur in severe cases rather late in the disease, and is usually dependent on an ascending infection by pus-forming organisms in the mouth. The more rigid the care of the mouth the less is the liability to this complication. Its occurrence is an indication for the use of alcohol or for an increase in its dose if the patient is already taking it. Either ice or a flaxseed poultice may be applied, preferably that which affords the more relief to pain. Incision may, or may not, be necessary.

Periostitis, Orchitis.—Periostitis and orchitis, also late complications, are more apt to be due to the typhoid bacillus and usually subside under treatment suitable to such inflammation apart from typhoid or syphilis. I cannot now recall a case in which incision proved needful, though such occur. Probably in these cases there is a mixed infection.[8]

Mastitis.—I have never seen mastitis. It may or may not suppurate. Its treatment is the same as when it occurs independently of typhoid.

Otitis.—Otitis, largely, as I believe, preventable by rigid care of the mouth, is to be treated practically in the same way as when it arises under other conditions.

Gall-bladder Affections.—Cholecystitis, with or without gall-stones, and perforation may occur either as complications during the disease or as sequelæ, even many years after the general infection. The treatment of perforation is always surgical, and if prompt and skillful is apt to be curative, more so than intestinal perforation, bile, even if mixed with pus, being far less noxious to the peritoneum than fecal matter.

If cholecystitis be suspected, surgical counsel should be had. Whether a prompt operation should be done must depend on the urgency of the symptoms and the state of the patient. No absolute rule can be laid down. Acute inflammation may subside spontaneously, with loss of all symptoms, permanently or for a time. There are accumulating data which indicate the frequency of the infection of the gall-bladder in typhoid fever. The use of the duodenal tube has demonstrated the presence of typhoid bacilli in the duodenal contents in certain individuals known or suspected to be typhoid carriers after recovery from the disease. The recovery of typhoid bacilli is apparently much simpler from the duodenal contents than from the stools. Operation has been performed upon a number of these typhoid carriers, some with and some without symptoms of gall-bladder disease. Final judgment cannot yet be passed upon this method of procedure of the treatment of chronic typhoid carriers. Apparently it is not always successful.

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[8] Typhoid osteomyelitis and typhoid perichondritis of the ribs frequently require surgical intervention even though due to a pure culture of the typhoid bacillus. In such cases very radical excision of the diseased area is necessary or relapse and further operation will be required.—Editor.

Those interested in the surgical aspects of typhoid, not only those referred to in this article, but also those so rare that it has not seemed worth while to detail them here, will do well to consult Keen's *Surgical Complications and Sequelæ of Typhoid Fever.*

Phlebitis.—Phlebitis, one of the more common sequelæ, is to be treated precisely as phlebitis arising under other conditions. Moist heat certainly promotes comfort during the early and active stage, even if it is uncertain whether it exerts a directly beneficial influence on the process. Moist heat is best applied by the flaxseed poultice, old-fashioned though it may be. When the saphenous vein is occluded, the whole thigh or even leg may be enveloped in the poultice, which should be renewed every two hours. The cooling of the poultice can be delayed by putting one or more Japanese hand-stoves (Kiro) over it. Large swelling will automatically tend to limit or do away with active motion, which it would seem reasonable to believe tends to enhance the chief danger of phlebitis, clot detachment and pulmonary embolism. Caution is to be exercised in the use of massage after the subsidence of active symptoms. It should be begun in a light form below the plugged vessel, which is to be let severely alone, certainly until cording has entirely or largely disappeared. The gentle support afforded by a well-fitting bandage made of flannel, cut bias, or by the Bender bandage, so-called, will be found useful until the old channel is fully reopened or adequate new channels are formed.

Tender Toes.—Tender toes are to be protected from the contact of the bedclothes by a cradle. A 25 per cent alcoholic solution of menthol applied locally may yield marked relief.

Typhoid Spine or Spondylitis.—From a therapeutic point of view, early recognition followed by prompt and efficient fixation are the important things.

Posttyphoidal Psychoses.—Psychoses following typhoid have a good prognosis. Whether asylum or sanatorium treatment is desirable must depend for decision on the circumstances and features of the individual case.

Furunculosis.—Furunculosis may be a very painful and distressing complication. It may be due to the pus-forming organisms, to the Bacillus typhosus, or to both combined. The utmost cleanliness of the skin is to be enforced and the foci are to be opened and drained, if necessary, as soon as ripe. If the boils are caused by the staphylococcus or other common pus-producers, an autogenous vaccine is indicated. If caused by the Bacillus typhosus it would seem rational to use in severe cases an autogenous vaccine of that organism, though I have not been able to find reports of cases in point.

So also in rebellious localized lesions due to the typhoid bacillus such a vaccine should be tried. Moffitt reports a case of obstinate, recurrent bone lesion which repeated operations failed to cure. An initial dose of 40,000,000 heterologous typhoid bacilli caused distressing general reaction with depression and malaise for days. Later, treatment was resumed with 1,000,000, gradually increased to 100,000,000, followed by final recovery.

Relapse.—Since relapse is a reinfection, the treatment of relapse does not differ from that of the original disease. As far as we now know, we have no means of modifying the immune processes of the body in typhoid fever, except in so far as they are modified by general measures, such as rest, diet, etc. Consequently it is impossible to prevent a relapse.

Treatment During Convalescence.—This, unless the attack has been very mild, is likely to be tedious. The patient is left empty, swept, and ungarnished. If he has been liberally fed during the fever, the loss in weight will not be very great; fully as much, if not more, in muscle than in fat. For at least two weeks after the subsidence of the fever any article of diet leaving irritating residue should be avoided, lest perforation be encouraged. The change in diet is quantitative, rather than qualitative. If, however, he has been fed exclusively on liquids, the change should be in both directions. I note that Forchheimer encourages his convalescents to acquire the objectionable habit of chewing gum to allay their pangs of hunger, and naïvely says that it does no harm. It seems to me more rational to forestall the pangs of hunger by allowing chewable and innocent food. Anyway, I would rather at the dreadful day of judgment face the accusation of having delayed somewhat the convalescence of my patient than of having taught him to chew gum and live on his own saliva. The gain in weight, which I have seen exceed two pounds a day, is at first mainly in fat. Muscle tissue is not replaced until it is used. A sensible procedure, concerning which no definite rules can be laid down, is to permit the nurse to carry out carefully graded massage and passive exercises. An intelligent nurse will incorporate these into the daily routine without its being noticed by the patient. When the sponge baths are no longer required for high temperature, more time can be taken with the daily morning bath and the evening attention. Such a course of massage and passive exercise prepares the patient for the activity which is to follow shortly and spares him a great deal of unnecessary muscle pain. Nervous strength may be the last to return. Nervous overfatigue is to be carefully avoided, whether from injudicious, or too many, visitors, or other cause. A fool visitor or a domestic or business worry can produce moderate elevation of temperature and retard recovery.

The consciousness of daily returning strength and an actively efficient digestion ordinarily help to reconcile the patient to any restrictions which are placed upon him. He sits up, first on a bed-rest, then in a chair at the bedside, then in the sunshine at an open window, with a daily increase in time, provided he thrives on it. I have repeatedly seen slight elevation of temperature persist until the patient is allowed to sit up. This is what may properly be called "bed fever." Other causes of temperature are to be sought for and eliminated before increasing activity. One of the chief of these is fecal retention, for which a mild laxative may be given by the mouth if full relief does not follow an oil or suds enema. Nothing like a fixed rule can be laid down as to how soon ordinary life can be resumed. The age of the patient, the severity of the infection, his individual reparative power, all the circumstances of his life, including the character of his work, his attitude toward it, his ability to abstain from a gainful occupation with that peace of mind which is so conducive to nutrition—all these things are to be considered. It is sometimes a year before he is good for much, well enough to resume an arduous and exacting calling; and yet financial considerations sometimes necessitate earlier resumption of work than is well or wise. Other things being equal, full power will be recovered more rapidly by the muscle than by the brain-worker. Convalescence is apt to be very slow in patients contracting the disease at or after middle life, I suppose because all vital processes are then slacked up. If feasible, a thorough change of scene with the maximum of outdoor life is desirable before the return to ordinary life.

PROPHYLAXIS OF TYPHOID FEVER BY MEANS OF VACCINES

Frederick F. Russell

Historical.—The history of the subject is closely identified with the development of our knowledge of immunity. As all early theories led to no clear-cut explanation of the well-recognized condition of immunity which almost invariably follows an attack of typhoid fever they have been either abandoned or profoundly modified.

The fundamental fact on which the entire procedure rests is that one attack, with rare exceptions, protects the individual for life. Osler says that "of 2,000 cases of enteric fever at the Hamburg General Hospital only 14 were affected twice, and but 1 person 3 times. In 500 of our own cases, in which special inquiry was made as to a previous attack, it was found to have occurred in 11 or 2.2 per cent."

The earliest attempt to produce immunity artificially against typhoid fever was made as long ago as 1886 by Simmons and Frankel some six years after the Bacillus typhosus had been discovered by Eberth. They used small laboratory animals, and succeeded in increasing the resistance to lethal doses of bacteria. Later their work was confirmed and extended by Beumer and Piper, and in 1888 by Chantemesse, Widal, Sanarelli, and others.

Little or nothing came of these early experiments, largely because of the impracticability of using living bacteria on man, and because there was then no satisfactory method of determining the existence of immunity in human beings, or of estimating its degree by examination of the blood serum.

In 1892 Brieger, Kitasato, and Wassermann found that the use of living bacteria was unnecessary, and that a high degree of immunity could be produced by killed cultures. In 1893 and 1894 R. Pfeiffer reported his investigations on the nature of the immunity in typhoid fever and cholera, and elaborated a test for the presence of the bacteriolytic protective bodies in the blood which has since become classic under the name of the Pfeiffer phenomenon.

In 1896 Gruber and Widal discovered the presence of agglutinins in the blood, and as a result our knowledge of changes in the blood serum during and subsequent to typhoid fever increased rapidly.

In the latter part of this year (1896) Pfeiffer and Kolle, using killed cultures of the bacillus, immunized 2 men against typhoid fever, and made complete and comprehensive studies of the changes in the blood serum during the progress of immunization.

Although their report covers only 2 cases, it is most convincing because of the completeness of the investigation; for they found, even after a single dose, not only an increase in the agglutinins, but also a marked increase in the bacteriolytic power of the blood. In this paper the authors suggested the use of vaccine to limit the spread of epidemics in civil life and in armies during war.

A short time before Pfeiffer and Kolle's results were announced Sir A. E. Wright, at that time professor in the Royal Army Medical College at Netley, England, published a paper entitled "On the Association of Serious Hemorrhages with Conditions of Defective Blood Coagulability," and in the course of his experimental work on this subject he inoculated 2 men with killed typhoid bacilli. The inoculation seems, however, to have been an incident in a research upon another subject. It served, nevertheless, to demonstrate the harmlessness of inoculating man with dead typhoid bacilli. The following year, 1897, he reported upon the inoculation of 17 persons, and the resultant changes in the blood serum produced by the immunization. It is in this paper that Wright mentions Haffkine's suggestion to him, made a year previously, that the method of vaccination with bacterial cultures, which had been so successfully used in the prophylaxis of cholera in India, might be applied to the prevention of typhoid fever. This publication makes it clearly evident that Wright had become convinced of the value and practicability of prophylactic inoculation, since he, at that time, suggested its use among physicians, surgeons, and the attendants of hospitals, and also recommended it for armies.

The present campaign of vaccination against the disease dates from the publication of this paper. To be sure, it had previously been suggested by other investigators, but with little result. Wright continued his work with enthusiasm both in India and Great Britain. About 4,000 men of the British Indian Army were inoculated by him in 1898 with excellent results. Colonel Leishman had reported upon the inoculation of about 100 of the attendants at the Barming Asylum, Maidstone, which was made about this time; and here, too, the results were highly encouraging, since no cases occurred among the inoculated. This was in marked contrast to the large number appearing among the unprotected. Soon after, in 1900, came the Boer War, when Wright convinced the War Office of the desirability of using prophylactic immunization upon the English troops. Voluntary inoculations were authorized, and Wright, assisted by Leishman, prepared some 400,000 doses of vaccine; though it is believed that not more than 100,000 men received one or more doses. Where it was possible the troops were inoculated before leaving England; yet many received the prophylactic while en route to South Africa, or in the field after arrival.

Regarding the 100,000 men reported to have received one or more inoculations no complete statistics have yet been published, and it is improbable that they will ever appear, as the extreme difficulty of collecting statistical data under such conditions can be readily appreciated. We do know, however, that there were 57,684 cases of typhoid fever with 8,022 deaths among an army of 380,605. This gives a morbidity rate of 151.56 per 1,000, and a mortality rate of 21.08, ratios which differ but slightly from our own in the Spanish War, where no vaccine was used.

This is shown in the table on the following page.

Wright attempted to collect statistics of typhoid fever both among the inoculated and the unprotected; but as his figures cover much less than half of the number of troops employed they failed to carry conviction.

TABLE I—VACCINATED AND UNVACCINATED TROOPS

Troops	Total Strength	Cases	Ratio per 1,000	Deaths	Ratio per 1,000
English Army, Boer War, 1900 to 1903	380,605	57,684	151.56	8,022	21.08
American Army, Spanish War	107,973	20,738	192.6	1,580	14.62

His results are set forth in the following table:

TABLE II—BOER WAR, ENGLISH TROOPS, WRIGHT'S STATISTIC.

Troops	Number	Cases	Ratio per 1,000	Deaths	Ratio per 1,000
Vaccinated	19,069	226	11.84	39	2.04
Unvaccinated	150,231	3,739	24.88	?	?

He considered the incidence of the disease was diminished about one-half, and the mortality even more; but his conclusions, based, as they were, upon incomplete returns, were not accepted by his colleagues in the service, and the whole matter was in considerable confusion. It was made still worse by the publication of unfavorable reports, some asserting that the vaccine did no good, others maintaining that it actually increased the number of cases and deaths.

As a result the British War Office suspended the practice of inoculation and appointed a commission to reinvestigate the whole question. This may be said to terminate the first period in the history of the subject, and at its conclusion quite naturally we find the entire procedure viewed with skepticism.

In South Africa antityphoid vaccination had undoubtedly failed to give the hoped-for protection. To explain the relative failure Wright brought forward the doctrine of the negative phase. From experience gained in making determinations of the opsonic index during the course of various infections and after the administration of vaccines, he concluded that there was a period during which the content of opsonins in the blood was decreased, and that this drop in the curve occurred after the administration of each dose of vaccine; this was called the negative phase in the progress of immunization. If the dose were not repeated too early, or too large a dose administered, the negative was followed by a positive phase leading to the high tide of immunity. A corollary of this state was a temporary increase of susceptibility to infection so long as the opsonic content of the blood remained below the normal. Wright believed this condition occurred in typhoid, and advised against vaccination when the individual might be exposed to infection before the immunization had been accomplished. Most of the inoculations in South Africa having been made under such conditions, this theory gave a plausible explanation of the poor results obtained. For a time the idea of a dangerous negative phase gained credence throughout the medical world.

Subsequent experience has proved the fallacy of this idea of increased susceptibility, and has also furnished the true explanation of the poor results. For these advances we are indebted to the work of Colonel Sir Wm. B. Leishman and his assistants. In a series of publications in the *Journal of the Royal Army Medical Corps* are related the various modifications made by Leishman of the original Wright vaccine, the most important of which was the change in the temperature used to kill the cultures. For many years 60° C. for one hour had been considered the thermal death point for the Bacillus typhosus, but from studies made in Leishman's laboratory it was found that 53° to 54° C. was sufficient, since which time the higher temperature has not been used. In the Harben Lecture Leishman informs us of the method used in preparing the vaccine for South Africa, and it appears that not infrequently even higher temperatures than 60° C. were used, and that, in his opinion, much of the vaccine sent to South Africa had been rendered practically inert from overheating during its preparation. The poor results of the Boer War were due, therefore, not to a negative phase of increased susceptibility but simply to failure of a defective vaccine to confer sufficient immunity.

German experience with antityphoid vaccine has been described in considerable detail, and the results may be summarized briefly. Typhoid fever had prevailed extensively among the German colonial troops in southwest Africa during the Herero Rebellion.

The usual sanitary measures had all been applied, but without material results. The military authorities referred the matter to Professor R. Koch for solution, and it was in accordance with his recommendations that vaccination of all possible volunteers was undertaken. A vaccine was prepared at the Institute for Infectious Diseases in Berlin, and about 7,000, or rather less than one-half, of the troops volunteered for treatment. Judged by present standards the dose used was large, and the resultant reactions severe. The amount of protection conferred was only enough to reduce the number of cases among the vaccinated to about one-half, and the death-rate rather more, as the disease, when it occurred, was not so fatal among the vaccinated.

American experience dates from 1908, when the writer was delegated by General Robert M. O'Reilly, at that time chief of the medical service of the Army, to investigate the subject in all its aspects. A visit was made to Colonel Leishman's laboratory at the Royal Army Medical College, London, and to the Institute for Infectious Diseases, Berlin, for the purpose of studying the methods already in use. On returning to this country a method was elaborated for our own service, which combined parts of both the English and German methods.

Preparation of Vaccine.—The American vaccine, as finally decided upon, is prepared as follows: It is made from a single strain of bacillus (Rawlings), and the culture is grown on agar in flasks for eighteen hours. At first, when small quantities only were needed, test tubes were used, but as the quantities increased Kolle flasks were substituted, each with an agar surface equivalent to twelve tubes.

The culture used is plated out—a dozen colonies are fished on to double sugar-tubes, and from these macroscopic agglutinations are made. Any culture which fails to develop the characteristic appearance on double sugar, or to give a good agglutination, is discarded; from the remaining cultures agar slants are inoculated and the next day emulsified in a small quantity of broth; with this thick emulsion the Kolle flasks are inoculated by means of a large swab. If they show no contamination after eighteen hours' incubation the growth is washed off in a small quantity of salt solution, and, while a sample is being counted, the thick suspension is heated in large flasks in a water bath for one hour at 53° to 54° C.

The killed vaccine is diluted with large quantities of salt solution until the desired concentration, 1,000,000,000 to the cubic centimeter, is obtained. Finally 0.25 per cent of tricresol is added as a matter of safety. After aërobic, anaërobic, and animal tests have been made the vaccine is put up for shipment in hermetically sealed ampules of normal glass.

The aërobic and anaërobic tests for sterility are made with large quantities of vaccine, several cubic centimeters to each tube and plate; the animal tests consist in the inoculation of a mouse and guinea pig with 0.5 and 1.5 c.c. for the exclusion of tetanus spores, and a rabbit with three doses at ten-day intervals to determine the immunizing power of the vaccine. The average titer of the agglutinating rabbit serum obtained with the last eighteen batches of vaccine after thirty days was 1 to 18,000.

Morphological tests of purity, using Gram's stain, are made at each stage of preparation, and a few lots of vaccine have been discarded because of contamination with the Bacillus subtilis group, but none have ever been rejected because of the animal tests. They are continued, however, because of the occurrence of a number of deaths from tetanus in India after the administration of plague vaccine.

We have used agar cultures because of the ease of detecting contamination and to avoid the injection of extraneous materials contained in fluid media.

The vaccine is killed by heat rather than chemicals, using the least amount possible to obtain sterility, and it is protected against subsequent contamination by tricresol.

Our vaccine is essentially the whole body of the Bacillus typhosus, changed as little as possible in killing, suspended in a convenient quantity of salt solution. Such a vaccine has the merit of simplicity, is readily and easily prepared, and is constant in quality.

T. A. B. vaccine contains 1,000,000,000 typhoid bacilli, and 750,000,000 each of paratyphoid A and B in each cubic centimeter.

Unless the paratyphoid fevers are present in the locality there is no justification for the use of a mixed vaccine. These fevers are present, however, on the Mexican border and in Europe, and the T. A. B. vaccine has justified its use wherever these fevers are present. It is administered in the same way as the simple typhoid vaccine. The reactions, however, are a little more pronounced.

Directions for Use of Vaccine.—Three doses are given at seven- to ten-day intervals; the first dose contains 500,000,000 bacteria, the second and third 1,000,000,000 contained in 0.5 c.c. and 1.00 c.c. of fluid. In army practice the ten-day interval is used as most desirable, but in civil practice the seven-day interval is often more convenient; thus bringing the three doses on three successive Saturday afternoons.

Experience has shown that the most suitable hour of the day for vaccinating applicants is late in the afternoon, since the local and general reactions do not usually appear until four or five hours after, at which time the patient is ready to retire, and by morning the entire reaction may have passed. It is wise to caution against active exercise, such as riding or tennis, and also against the use of alcohol in any form, since both tend to aggravate the condition.

The vaccine is injected subcutaneously, and not into the muscles nor into the skin; this is necessary to secure slow absorption; deep muscular injections, because of the rapid absorption, are more apt to produce severe reactions and pain on movement.

The best location for the injection is the outer surface of the arm over the insertion of the deltoid muscle, where the subcutaneous tissue is abundant. Sterilization of the skin is secured by tincture of iodin.

In the army none but the healthy are immunized, any illness automatically postponing the vaccination. Postponement, however, rarely occurs, as only healthy men are accepted for service. In civil life conditions are different, and it may be necessary at times to immunize invalids. Each case must be considered on its own merits, and by using a greater number of smaller doses it is probable that many not in good health may be safely immunized. The routine test, of course, of a successful immunization is the presence of a good Widal reaction.

Reaction.—Each dose of vaccine is followed by a local reaction which varies little either with the size of the dose or the idiosyncrasy of the individual.

Usually there is a red and tender spot about 2 inches in diameter at the point of inoculation. This first appears in six to eight hours and reaches its full development in about twelve; it then gradually subsides, and disappears, as a rule, in forty-eight to seventy-two hours. It happens occasionally, especially in children, that there is little or no local reaction, but this is a rather rare occurrence. Occasionally the red and swollen area may be quite extensive and extend from above the point of inoculation to the elbow or even halfway to the wrist. At times it also extends upward to the axilla, and the lymph-nodes may be swollen and tender on pressure. The symptoms referable to glandular swelling disappear in about twenty-four hours and are never followed by permanent enlargement or suppuration.

Such extensive local reactions are not particularly painful, and the men are able to use the arm for light work without discomfort; it has never been necessary to use any local application or to place the arm in a sling, and recovery occurs about as quickly as after the usual reaction. This type of reaction is fortunately quite rare.

At the site of inoculation a small, hard, bulletlike nodule may occasionally persist for several weeks before subsiding; no treatment is necessary, as it invariably disappears, leaving no sign.

The general reaction varies in its symptoms much more than the local. In children and in many adults it may be truly said to be absent. The milder form is characterized by a transitory headache and a feeling of weariness lasting from two to three hours to a day. Slightly more marked general reactions are evidenced by considerable headache and a decided feeling of lassitude lasting until about noon of the following day. Occasionally there are chilly sensations without much, if any, rise of temperature. A few men have complained of nausea or diarrhea lasting for a few hours to a day. In the average case the mild reaction resembles the feeling of discomfort which precedes an acute cold in the head.

Moderate reactions are those characterized by a rise of temperature varying from 101° to 103° F. Chills may occur, and the symptoms described above may exist in more pronounced form. Moderate reactions follow about 2½ per cent of all doses, occurring with about equal frequency after the first and second doses, but much less often after the third dose.

A reaction producing a temperature of 103° F. or over is classed as severe. In many instances there is also a chill or chilly sensations, with more or less headache, nausea, vomiting, or herpes labialis; in the early days when large doses were administered albuminuria was occasionally present after severe reactions; to-day albuminuria is extremely infrequent.

It has already been stated that active exercise or alcoholic indulgence may determine a severe reaction; deep injections into the muscle, or wholly or partly into some vein, permitting of quite rapid absorption, are believed to be responsible for the severe reactions which come on almost immediately after inoculation. They are easily prevented by remembering the injunction to introduce the vaccine in every case subcutaneously; when the hypodermic injection is properly given the dose causes a visible and palpable subcutaneous swelling for a few minutes. For the other severe reactions there is no better explanation than the supposition of great susceptibility of the individual to the Bacillus typhosus; and it is reasonable to believe that such individuals would, if infected, suffer severely from typhoid fever.

The general reactions following the first 128,903 doses administered to soldiers have been tabulated, and show that the severe type of reaction occurs after only one to three doses per thousand.

TABLE III—REACTIONS TO DOSES

Dose	Number of Doses	Per Cent Absent Reaction	Per Cent Mild Reaction	Per Cent Moderate Reaction	Per Cent Severe Reaction
1	45,680	68.2	28.9	2.4	0.3
2	44,321	71.3	25.7	2.6	0.2
3	38,902	78.0	20.3	1.5	0.1

The reactions following the administration of the T. A. B. vaccine are a little more pronounced. Agglutinins begin to appear on the fifth to eighth day and increase rapidly; ten days after the third dose the Widal is often present in dilutions of 1:5,000, and occasionally the serum shows a titer of 1:10,000, or even 1:20,000. Only rarely does it fail to exceed 1:600. The rise in opsonins follows quickly, and their increase is quite as striking as the development of agglutinins. Wright's method of estimating the opsonic index is inapplicable in typhoid because of the lytic and agglutinating action of the undiluted serum upon the Bacillus typhosus. Resort was had, therefore, to the dilution method of Neufeld, which proved quite simple and satisfactory. The serum is diluted as for agglutination tests, and to equal quantities is added a suitable salt solution suspension of typhoid bacilli; the mixture is incubated at 37° C. for one hour. A suspension of guinea pig leukocytes obtained by injecting aleuronat into the abdominal cavity is then added in equal quantity to each tube, and this mixture is again incubated for an hour; salt solution controls being prepared at the beginning and end of each set of tests. When the incubation is completed smears are made from sediment in each tube. The phagocytic titer of the serum is determined by ascertaining the highest serum dilution in which the phagocytosis is positive, that is, in which it exceeds the spontaneous phagocytosis occurring in the controls. Perfectly uniform and consistent results have been obtained by this method. The phagocytic titer is never so high as the agglutinative, nor does it remain up as long; but it has always been well marked and quite constant. A titer of 1:1,000 or 1:2,000 is quite common, while the curve occasionally rises to 1:5,000 or even 1:6,000. It drops at first rapidly and then more slowly, but may still exceed the normal after the lapse of a year.

Other vaccines have from time to time been proposed. The older vaccines of Neisser, Shiga, Bassenge-Rimpau, and Wassermann are merely of historic interest. The English and American vaccines are refinements of those of Wright and of Pfeiffer and Kolle. In France the vaccine of Vincent has been used most frequently. It is prepared as follows: Several strains isolated in the neighborhood in which the vaccine is to be used are grown on agar twenty-four to forty-eight hours; the growth is taken up in salt solution and kept at 37° C. from two to four days; after centrifugation the supernatant fluid is sterilized by being shaken with ether, which is then allowed to evaporate. Three or four injections are given at short intervals. The results obtained are excellent, and will be referred to later.

Metchnikoff and Besredka in 1911 proposed the use of a living sensitized vaccine. They have conducted the most extensive investigation of recent years, using chimpanzees as test animals. They found that in these animals killed vaccines were powerless to prevent typhoid fever when overwhelming doses of infectious material were used, but that prophylactic immunization with sensitized living bacilli gave them power to resist even large doses, such as may occur in milk-borne epidemics. Interesting and valuable as this work of Metchnikoff and Besredka undoubtedly is, it nevertheless deals with a limited number of apes, and for practical purposes cannot, in the opinion of the writer, be compared to the work in the military service with nearly 200,000 human beings. They, however, all contain living bacilli, which are capable of multiplication outside of the body and there is, therefore, some danger from their general use. Since ample protection may be obtained with killed vaccines, their use is not believed to be necessary.

It is evident from Tables VI and VII that our present vaccine is conferring immunity in as great a degree as has ever been done by any vaccine. It is certain that in the military service typhoid prophylaxis is quite as successful as vaccination against smallpox, our old ideal of what a prophylactic measure should accomplish. It is evident from this that the opinion held by many scientists that living vaccines and viruses are superior to dead vaccines, and that a high degree of immunity can only be conferred by the use of living vaccines, must be reconsidered at least in reference to typhoid and paratyphoid fevers; our experience has definitely demonstrated that the immunity conferred by dead typhoid bacilli is in no way inferior to the immunity against smallpox conferred by living vaccine virus. Sensitized vaccine in this country has been prepared and used by F. P. Gay, and its use in institutions reported upon by Force, who used a sensitized, killed vaccine prepared for him by Gay in the following manner:

"The 'Army' strain (long cultivated on laboratory media) of B. typhosus was used. A 24-hour bouillon culture was planted on 10 large, flat-sided (Blake) bottles of agar, incubated at 37.5° C. for 36 hours. The growth was then washed off in sterile salt solution, 100 c.c. being the total volume. One c.c. of a strongly agglutinating serum (1:20,000) was added to this emulsion, and it was allowed to stand one night in the icebox. Equal parts of absolute alcohol were then added to the suspension, the organisms quickly flocculated out completely, and after centrifugalization in a high-speed centrifuge the supernatant fluid was poured off and the residue transferred to a sterile evaporating dish and dried in a partial vacuum over night. The residue was then scraped off carefully to avoid any contamination, put into a grinder and ground for one hour. This fine bacterial powder when kept sterile can be used at any time, making up a suspension of 1/16 mg. to 1 c.c. carbolated 0.85 per cent salt solution."

Force believes the immediate general and local reactions are milder than those following unsensitized vaccines, a statement we have been unable to confirm. Little is yet known about the degree and duration of the immunity conferred by living or killed sensitized vaccines. These are comparatively new, and it may be well to summarize the reasons advanced for using them. The first, that good protection cannot be obtained from unsensitized vaccines, falls to the ground, now that American army experience has demonstrated the contrary. The second reason, that the reaction is less severe, is still undecided. In a small series of inoculations carried out upon physicians at the Army Medical School the sensitized vaccine produced at least as severe reaction as the unsensitized. Further investigation is required to demonstrate the degree and duration of the protection conferred.

Lipovaccines were proposed and used by Le Moignic in France during 1918. Whitmore in the United States was an advocate of their use. It was hoped that a large quantity of bacilli might be suspended in oil, and be given in a single dose, since it was thought probable that absorption would take place gradually over a long period. Unfortunately animal tests have shown, when the animal was killed and the lesion examined, that the bacteria settle out of the oil very quickly and the absorption is probably quite rapid. As gaged by the presence of agglutinins, the results are greatly inferior to saline vaccines, although no doubt some protection may be achieved.

Vaccination by Mouth.—Besredka[9] reviews the work of Vaillant, who investigated the merit of the method in an area in northern France, where the disease is endemic. Out of a total population of 2,000, 1,236 were given the pill of bile and tablet of killed typhoid bacilli. It was given before breakfast on three successive days; 173 persons were given a vaccine subcutaneously. The results reported were as follows: Following the administration of Besredka's vaccine by mouth, 1,236 persons (0.17 per cent) developed the disease; among those vaccinated subcutaneously 173 persons (2.3 per cent); while among the unvaccinated the incidence of the disease was 7.7 per cent. No unpleasant symptoms, other than slight colic and headache in a few cases, were seen, and these were not sufficient to interfere with the regular work of the treated. Although the number of persons observed is rather small, Besredka believes the results at least equal to those obtained by subcutaneous vaccination.

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[9] Paris Med., June 3, 1922.

The use of Besredka's bile vaccine is based upon the idea that since infection takes place through the mouth, the oral administration of the vaccine will bring about a local immunity of the intestinal mucosa, which will be adequate for protection. This is, of course, at variance with the commonly accepted idea of antityphoid immunity. There does not seem to be as yet any valid proof of the existence of a local intestinal immunity. The results so far obtained, however, are suggestive, and the question needs further study. Since typhoid is a disease of human beings only, the experimental solution of these questions in the laboratory is not simple.

Results Obtained in American Army.—Vaccination was voluntary during 1909, 1910, and the greater part of 1911, since which time it has been compulsory for all members of the service under forty-five years of age. In 1909 volunteers were quite difficult to obtain, the greater number being members of the Medical and Hospital Corps of the Army, together with their families, friends, and servants. At the end of that year 1,887 persons had been immunized, most of whom received three doses of the prophylactic. The following year, 1910, volunteers were easier to obtain, and 16,000 persons were treated. During the first part of 1911 volunteers continued to present themselves in increasing numbers, until finally immunized men came to be present in practically every garrison in the United States proper. The measure was no longer strange to the Medical Corps, nor to the enlisted personnel of the Army. We noticed, however, as with all voluntary measures, a great inequality in different garrisons, depending upon the interest and enthusiasm, or lack of it, of the surgeon and the commanding officer.

During the preliminary period of voluntary vaccination records of some 20,000 cases had been collected, clearly demonstrating the safety of the method. It caused comparatively few severe reactions, and no vaccination, no matter how severe the immediate reaction may have been, was followed by any permanent injury to the individual. The degree of immunity conferred, as judged by the usual laboratory tests, was identical with and equal to that following an attack of typhoid fever. The comparative absence of typhoid fever among vaccinated troops, as compared with the unvaccinated, was beginning to confirm the tests for immunity made in the laboratory (see Table VI, years 1909, 1910, and 1911). There was, therefore, abundant proof that the vaccine used in the Army was both harmless and effective.

The introduction of compulsory vaccination occurred in March, 1911, upon the mobilization of a maneuver division in Texas. For the reasons already given it was apparent that it was feasible and practicable to vaccinate the entire 20,000 men in the field. That it was also desirable was immediately apparent from an examination of the reports of typhoid fever in the Spanish-American and other recent campaigns.

TABLE IV—TYPHOID FEVER IN RECENT CAMPAIGNS

Troops	Strength	Typhoid Cases	Typhoid Deaths	Killed in Action or Died of Wounds	Died of Disease	Wounded	Missing
Franco - German War, German Army	......	73,393	6,965	28,269	15,240	68,498	12,854
Spanish - American War, American Army	107,973	20,738	1,580	243	2,565	1,445	.....
Boer War, British Army	380,605	57,684	8,022	7,702	13,250	22,829	.....
Russo - Japanese War, Russian Army	......	17,033	....	34,000	9,300	141,800	.....

Table IV gives all available information regarding losses from typhoid fever in comparison with losses from other causes in four modern wars, and demonstrates how imperative it was that every possible effort should be made to prevent any recurrence of such epidemics.

The manner in which typhoid fever became epidemic in military camps in 1898 is well known, and the military authorities realized fully that in spite of much improved measures of camp sanitation the disease might again prevail sufficiently to handicap some portion of our forces should they be called upon for actual warfare. It was with full confidence in the measure, and a firm conviction as to its efficacy, that vaccination was made compulsory for the maneuver division.

The immunization of the 20,000 men in the field on the Southern border was carried out promptly and without any special difficulties. The single complication reported was the development of a musculospiral neuritis in one man.

The results obtained are shown in the following table, in which the camp at Jacksonville, Florida, in 1898, is compared with the camp at San Antonio, Texas, in 1911:

TABLE V—1898, SPANISH-AMERICAN WAR

Camp at Jacksonville, Florida

Number of Troops	Cases of Typhoid Certain	Certain and Probable	Deaths from Typhoid	All Deaths
10,759	1,729	2,693	248	281

1911, Camp at San Antonio, Texas

Number of Troops	Cases of Typhoid Certain	Certain and Probable	Deaths from Typhoid	All Deaths
12,801	2	....	....	11

At Jacksonville there were assembled 10,759 men, among whom there were 1,729 undoubted cases of typhoid, and, including those in which a diagnosis of typhoid was probable, there were 2,693 cases, with 248 deaths. This camp lasted approximately as long as the camp at San Antonio in 1911; both camps were situated in about the same latitude, and each had artesian well water of excellent quality, yet in 1898 there were over 2,500 cases of typhoid fever, with 248 deaths, and in 1911 only 2 cases, with no fatalities. We know that the immunity was not due to lack of exposure, since there were reported to the health office 49 cases of typhoid fever, with 19 deaths, among the civil population of the city of San Antonio during the period of encampment.

Soon after the completion of the successful vaccination of this division it was decided to immunize all army recruits at the time of enlistment into the service. This was ordered in June, 1911, since which date all men on joining the service are vaccinated against smallpox on one arm and against typhoid fever on the other. Only on rare occasions has it been necessary to postpone the second or third doses of the typhoid prophylactic because of vaccinia. Some 2,000 to 3,000 recruits have been immunized monthly since June, 1911.

The last step was the extension of compulsory prophylaxis to all persons in the service under forty-five years of age, and this was ordered on September 30, 1911. In the United States proper the order was not fully executed before January 1, 1912, and in the Philippines not until the first quarter of 1912.

The full effect of these measures can most clearly be set forth in tables and charts of the typhoid fever experience of the army year by year. It is necessary to a correct interpretation of these tables to remember that voluntary immunizations began on a small scale in 1909; that compulsory vaccination was introduced gradually in 1911, but did not include the entire army until 1912.

There are three standards by which to judge of the degree of improvement: the number of cases admitted to sick report, expressed as the admission rate per 1,000 of mean strength; the number of deaths, expressed in the same manner; and the constantly non-effective rate, which is a statement of the average number of men in each 1,000 incapacitated for duty by typhoid fever each day during the year. It is generally acknowledged that the constantly non-effective rate is the truest measure of the gain or loss of efficiency from any or all causes.

Table VI gives all data pertaining to enlisted men stationed within the continental limits of the United States. There is a most decided and significant drop in the ratios for cases and deaths in 1911, 1912, and 1913.

TABLE VI—TYPHOID FEVER (UNITED STATES), AMONG ENLISTED AMERICAN TROOPS

Year	Mean Strength	Absolute Cases	Number of Deaths	To Each 1,000 Soldiers of the Command, the Ratios are:	
				For Cases	For Deaths
1904	43,940	247	12	5.62	.27
1905	42,834	153	13	3.57	.30
1906	40,621	230	12	5.66	.28
1907	35,132	124	7	3.53	.19
1908	46,316	136	11	2.94	.23
1909	57,124	173	16	3.03	.28
1910	55,680	129	9	2.32	.16
1911	55,240	44	6	0.80	.11
1912	58,119	15	2	0.26	.03
1913	59,608	2	0	0.03	.00

Table VII exhibits the number of cases and deaths occurring each year in the United States (continental) among both officers and men. It shows, also, the number, so far as ascertainable, infected before enlistment, and the number of cases and deaths occurring among the vaccinated each year since the introduction of vaccination.

TABLE VII—NUMBER AND PROPORTION OF TYPHOID FEVER CASES CONTRACTED BEFORE ENLISTMENT AND AMONG THE PROTECTED (UNITED STATES PROPER ONLY) OFFICERS AND ENLISTED MEN

Year	Total Cases	Total Deaths	Infected Prior to Enlistment	Among the Vaccinated	
				Number of Cases	Number of Deaths
1909	173	16	?	1	0
1910	129	9	?	4	0
1911	44	6	?	7	0
1912	18	3	5	6	0
1913	2	0	2	0	0

Table VIII differs from Table VI in including all persons in the service, officers as well as men, whether stationed at home or abroad during the War period. It covers the period from 1901 to and including 1918; this table includes a statement of all cases and deaths from typhoid fever occurring among the inoculated up to 1914. It demonstrates that the improvement was not confined to the United States, but held good throughout the army. For comparison the rates for males of the same age group, twenty to thirty, of the civil population of the ten original registration states, Connecticut, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Rhode Island, Vermont, and the District of Columbia, may be used. There is ample evidence that the rates in these older, more highly urbanized states, is lower than the average for the registration area, and the comparison, therefore, is conservative.

This table should make clear to any large employer of labor or responsible head of any institution or school how antityphoid vaccine would diminish the number of days lost annually from typhoid fever.

From these tables deductions may be made with safety; they are based upon accurate observation by thousands of physicians upon 4,000,000 to 5,000,000 men, and are as accurate as only great care can make them. They exhibit a sudden and decided drop in both morbidity and mortality

TABLE VIII [*]—RATE OF TYPHOID FEVER IN ARMY AND IN CORRESPONDING AGE GROUP IN CIVIL LIFE FOR PAST EIGHTEEN YEARS

Year	Army				Civil Deaths from Typhoid Fever. Age Group, 20 to 29 years. Rate per Thousand of Population	
	Number of Cases	Ratio per Thousand	Deaths	Ratio per Thousand	Total	Males
1900	531	5.75	60	0.43	0.46	...
1901	594	9.43	78	0.64	0.42	0.54
1902	565	8.58	69	0.86	0.40	...
1903	348	5.82	30	0.28	0.35	...
1904	247	5.62	12	0.27	0.33	...
1905	193	3.57	17	0.30	0.32	...
1906	347	5.66	15	0.28	0.32	...
1907	208	3.53	16	0.19	0.28	...
1908	215	2.94	21	0.23	0.28	...
1909[†]	173	3.03	16	0.28	0.23	...
1910	142	2.32	10	0.16	0.27	0.34
1911[‡]	44	0.85	6	0.09	0.23	...
1912	18	0.31	3	0.04	0.18	...
1913	4	0.04	0	0.00	0.18	...
1914	7	0.07	3	0.03	0.15	...
1915	8	0.08	0	0.00	0.18	0.17
1916	25	0.23	3	0.03	0.12	0.15
1917	297	0.44	23	0.03	0.11	0.14
1918	768	0.30	133	0.05	0.09	0.11

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[*] Russell, F. F. Journ. Am. Med. Ass., No. 25, lxxiii, 1863, Dec. 20, 1919.

[†] Voluntary vaccination against typhoid.

[‡] Compulsory vaccination against typhoid.

during the past few years, which corresponds with the increase in the use of antityphoid vaccine.

Table VIII can be analyzed in another way as follows:

TABLE IX—NUMBER OF PEOPLE FURNISHING A CASE OF TYPHOID FEVER, OR A DEATH FOR EACH PERIOD *

	Population Furnishing One Case	Population Furnishing One Death
Troops in Spanish War	7	71
Troops in World War	3,756	25,641
Restricted registration area 1917, civil life...	No record	7,143
" " " 1918, " " ...	" "	9,090

* Russell, F. F. Journ. Am. Med. Ass., No. 25, lxxiii, 1864, Dec. 20, 1919.

It is, indeed, remarkable that the mortality among troops, both at home and at the front where they were often deprived of all sanitary protection, should have shown a lower death-rate than found at home in the older states, where excellent water and sewer systems, and all other sanitary safeguards have been carried to a high degree of development.

When one compares the death-rates of the World War, the Spanish-American and the Civil Wars, the rates, based as these are on very large numbers of observations, are clean-cut and carry conviction. These are shown in the following table:

TABLE X—RELATION OF MORTALITY IN THE WORLD WAR TO THAT OF PREVIOUS WARS *

Disease	Number of Deaths That Occurred in Present War, Sept. 1, 1917-May 2, 1919: Average Strength Approximately 2,121,396	Number of Deaths That Would Have Occurred if the Civil War Death-Rate Had Obtained	Number of Deaths That Would Have Occurred if the Spanish-American War Death-Rate Had Obtained
Typhoid fever	213	51,133	68,164
Malaria	13	13,951†	11,317
Dysentery	42	63,898‡	6,382†

* Russell, F. F. Journ. Am. Med. Ass., No. 25, lxxiii, 1864, Dec. 20, 1919.
† Includes malaria, remittent and congestive fevers.
‡ Includes dysentery and diarrhea.

In the United States Navy similar results have been obtained; the number of cases, deaths, and days lost from sickness all show decided improvement. Among approximately 80,000 persons in the Navy who have received the full course of vaccine, only 7 authentic cases of typhoid fever have developed, and these were characterized by mild symptoms and rapid convalescence. In former years many cases had developed among midshipmen returning to the Naval Academy from holidays spent at home; yet none occurred in 1912, owing to the fact that all cadets had been vaccinated.

Similar results have been obtained in civil life, although no collected statistics are available to show it. Richardson and Spooner, Hachtel and Stoner, Brannan, and many others have used the vaccine both in hospitals and in private practice, so far as known, without untoward results and with good protection.

The state boards of health of Massachusetts, Virginia, South Carolina, and several other states now supply the vaccine gratis in their respective states. New York, Buffalo, Memphis, and many other city health boards have not only provided free vaccine, but have administered it to all volunteers.

The rule of the New York health department is to offer immunization to all members of the household whenever a typhoid patient is found. This practice has now prevailed sufficiently long to demonstrate that only good results are obtained. The New York Academy of Medicine has adopted a resolution urging that all persons in any infected family, and any person who has been exposed in any way to the disease, follow all the sanitary precautions usually taken in such cases, and subject themselves to immunization either at the hands of their private physician or of the department of health.

In addition to American statistics there is abundance of favorable evidence from the British Army in India, where antityphoid vaccination has been in use for a longer period than in any other part of the world.

In France during the past few years, mainly owing to the work of Vincent, professor at the French army medical college at Val de Grace, considerable advances have been made, especially among the colonial troops in Tunis and Algeria. Up to November, 1913, Labbé states 100,000 persons had been immunized without any untoward results, and with great reduction in the morbidity and mortality. He introduced, in November, 1913, a bill into the French Senate, which has since become a law, to make vaccination in the army compulsory, as it is in the United States.

The vaccination of *nurses* has rightly been regarded as a severe test, because of the high degree of exposure to the disease, due to their calling. Achard stated that during the past nine years 1,739 nurses, serving in a hospital with which he was connected, were vaccinated and that only 1 contracted the fever.

Enough evidence has been presented to prove that antityphoid vaccination is a comparatively simple and, when used on the healthy, a harmless procedure; that it gives rise to a very high degree of immunity closely approaching that conferred by typhoid fever itself and that it has been and easily can be used to immunize large numbers of persons; in fact, its administration to the masses is no more difficult than vaccinia.

Since the war, the increased use of vaccine in civil life has been noted.

In France, general vaccination throughout the republic has been advocated by the Minister of Public Health and by the Academy of Medicine (1921).

Achard reports that during the preceding fifteen months, he had treated 25 cases of typhoid—all were women, or youths, or elderly men, except 3 men who had been vaccinated while with the army. Of these 2 had very mild attacks, while the third had paratyphoid.

He notes, as others have in the United States, that since the War typhoid has been a disease of women rather than of men—a complete reversal of the former relationship.

Chauffard advocates general vaccination of the civil population, and suggests that the first immunization be given at the age of fifteen, the second at eighteen, and the third at twenty-one. He believes such a policy would gradually eliminate the disease.

Summary.—It remains merely to formulate a working plan for future guidance in its use.

Its use is definitely indicated:

1. In the Army, Navy, National Guards of the various states, and all volunteer organizations called into service in time of war.
2. Among the personnel of all hospitals, dispensaries, and Red Cross organizations.
3. In boarding schools, colleges, institutions of all kinds, asylums, prisons, workhouses, and the like.
4. In the camps of pleasure-seekers, explorers, engineers, and contractors. In all these instances its use is sufficiently obvious.
5. Among the inhabitants of cities or districts where the typhoid fever rate is continuously high.
6. Among travelers, especially such as leave sanitary cities for summer vacations in country districts and seaside resorts.
7. Among young adults, young persons, and children. Osler characterizes typhoid fever as a disease of youth and early life, and one which is not infrequent in childhood. It has been shown that children and young persons withstand the immunization rather better than adults; in fact, it rarely interferes with school or play.

The dosage recommended for children is based upon the body weight rather than the age; considering the average adult as weighing in the neighborhood of 150 pounds, a child weighing 50 pounds would be given one-third the dose. Should the fraction of the adult dose be inconvenient to measure in the hypodermic syringe it is better to give a little more rather than less. No harmful results have occurred in several instances in which a considerable overdose was given.

8. Among the members of the household where a case of typhoid fever occurs and all persons who in any way come into contact with the patient.

9. Voluntary vaccination of the non-immune population on the occurrence of an epidemic of typhoid fever. This has been done by Spooner, Hunt, Goldman, and others.

Hunt has pointed out how much may logically be expected from the use of vaccine during epidemics. In outbreaks due to an infected public water supply it is now the custom of the health authorities, as soon as the diagnosis is made, to sterilize the water with some form of chlorin. This, of itself, is the best measure to stop further primary cases. It will, however, have no effect upon the chain of secondary cases which follow in the wake of every epidemic. It is these contact cases which can be prevented by vaccination subsequent to the outbreak.

The question of vaccination in the case of those already infected, and in the incubation stage of the disease at the time, arises in this connection. A fair number of instances are known both in and out of the service where typhoid fever developed soon after vaccination, but it is not believed that there is any valid reason for thinking that any harm was done; and in many instances it is possible that the disease was rendered less severe. This is not unreasonable in view of the conclusions of Watters that the use of vaccine in the treatment of typhoid fever is promising, and merits investigation.

The question of *revaccination* has not yet received a definite answer, since the duration of the immunity conferred by our vaccine is not known. The immunity is greatest soon after immunization, and it no doubt gradually diminishes as after vaccination against smallpox. In the English service the effective duration of the immunity seems to be only two and one-half years. Some light is thrown on this by the Salem, Ohio, epidemic of 1920. Out of a total population of 10,305 there were 882 cases occurring within a period of three months. Among 210 ex-soldiers, aged twenty to thirty, there were only 3 cases, an incidence of 1 in 70; while among the female population of the same age group the incidence was 1 in 8. All these men had been vaccinated more than two years before and some of them three years before. The present practice in the Army is to revaccinate against both smallpox and typhoid fever at the commencement of each enlistment period, which is, at present, once in four years. This is done, not because we have definite knowledge that the immunity has disappeared, but for the reason that in the Army it would be unwise to depend upon anything less than the maximum obtainable. The general reactions after revaccination are given in the table on page 363, and are seen to be practically the same as after the original immunization:

The future may indicate that reimmunization against typhoid need not be done more often than revaccination against smallpox, that is, in childhood, youth, for military service, and upon exposure to infection.

At one time it was believed that the agglutination reaction would

Table XI—General Reactions Following Revaccination, January 30, 1914

Number of Doses		Absent	Per Cent	Mild	Per Cent	Moderate	Per Cent	Severe	Per Cent
First	500	359	71.8	127	25.4	13	2.6	1	0.2
Second	500	382	76.4	95	19.0	23	4.6	0	0.0
Third	500	417	83.4	71	14.2	10	2.0	2	0.4
Total	1,500	1,158	77.2	293	19.5	46	3.1	3	0.2

indicate the presence or absence of this immunity. The fallacy became apparent when it was noted that the agglutination reaction usually disappears in from six to eighteen months after typhoid fever itself, although the immunity remains, as a rule, for life.

In conclusion it may not be amiss to recall that vaccination is not the only measure to be used in the suppression of typhoid fever. Good, pure water supplies, proper sewer systems and purification plants, and all other general sanitary measures are imperative, and none should be overlooked. Antityphoid vaccination is a matter of personal hygiene rather than of general sanitation, and is useful in protecting the individual against accidental or unusual exposure or where sanitary safeguards are inadequate. At present vaccination is the only method offering protection against infection at all times and under all conditions. There is no occasion for conflict between the advocates of general and individual prophylaxis; one is as necessary as the other, and no one interested in the suppression of this disease can afford to ignore either.

We have now reached the stage in preventive medicine when it is possible to declare that deaths from typhoid fever are practically avoidable. Wherever state or municipal authorities fail to provide adequate sanitary safeguards the individual now has it in his power to obtain through vaccination almost absolute protection against infection. There is sufficient proof to justify physicians in urging upon their clientele, especially upon the young people and children, the use of the vaccine with just as much confidence and authority as has been used in urging vaccination against smallpox.

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CHAPTER XIII

DIAGNOSIS AND TREATMENT OF COLON BACILLUS INFECTIONS

Willard J. Stone

BACTERIOLOGIC CONSIDERATIONS

The B. coli communis was discovered by Escherich in 1885. The original culture was obtained from the bowel discharges of a breast-fed infant. This organism has been found widely distributed in nature, and is almost constantly present in the intestinal tract of man and many of the higher animals. It is often found in almost pure culture in the large intestine, but in the small bowel it grows as a rule in association with many other bacteria, the most important of which is the B. lactis aërogenes. The B. coli can be easily cultivated from the stools by any of the ordinary aërobic methods. It has been cultivated from the dejecta of infants in from four to eighteen hours after birth. It is probably identical with the B. neapolitanus of Emmerich and the B. pyogenes fœtidus of Passet.

Because of its widespread distribution in nature the B. coli, or, as it is commonly called, the colon bacillus, may occur as an etiologic cause in a variety of conditions, sometimes as the sole organism present and again in association with harmless saprophytes or with pathogenic varieties. It is one of the strange arrangements of nature which permits the development of a variety of organisms within the body in harmless contact with certain tissues, while, if transported to other tissues, the cells of which apparently are not sensitized or immune to their presence, their development there leads to tissue destruction. For example, the colon bacillus, while harmless when in contact with the cells of the intestinal mucosa, may produce a fatal peritonitis when developing in contact with the endothelial cells of the intestinal serosa.

There can be no doubt that the pathogenicity of the colon bacillus has been exaggerated. On the other hand, its frequent association with certain septic processes cannot be doubted. In appendiceal abscesses, in cholecystitis and cholangitis, in cystitis and pyelitis, in acute prostatitis, in peritonitis, in septicopyemic processes with multiple abscesses in soft tissues or bone, or in septic thrombus following abdominal operations, it is frequently found. There can be no doubt also of the great increase of the colon bacillus in the intestine during typhoid fever as well as during other pathologic ulcerative or obstructive lesions affecting the bowel. In fact, many writers, among them Sanarelli, are disposed to regard some of the pathologic changes ascribed to typhoid to the increased virulence assumed by B. coli in the presence of the typhoid bacillus.

The conditions necessary for the migration of the B. coli from the intestinal tract into the blood-stream or into the lymphatics, by means of which the organisms may be transported to more or less distant tissues, are probably intimately connected with trauma and separation of tissue continuity. For example, a rectal fissure, a tuberculous or carcinomatous ulcer, or small thrombi in vessels incident to surgical procedures may serve as the point of entrance. It is probably true that the organisms frequently reach the lymph tributaries to mesenteric glands, where their progress is stopped. Given, however, a temporarily lowered resistance, the organisms may overcome cellular activity in the glands and, reaching the blood-stream, be carried to other tissues. In this way may be explained the suddenness of onset of certain attacks of cystitis and prostatitis, following cold and exposure.

The lesions produced in animals by injection of B. coli are very similar to those produced by the B. typhosus. There are, however, distinct cultural characteristics by means of which B. coli can be differentiated from the B. typhosus and B. enteritidis. Among the most important of these are the following, mentioned by Jordan:

CULTURAL CHARACTERISTICS OF B. COLI, B. TYPHOSUS AND B. ENTERITIDIS

B. coli	B. typhosus	B. enteritidis (Gärtner)
Slightly motile short rod, often difficult to distinguish from micrococci, few flagella. Grows more rapidly in gelatin than B. typhosus. Produces acid and curdles milk. Indol is produced by most strains. Dextrose and lactose are fermented with gas production. Visible growth on potato.	Actively motile rod with numerous flagella. Milk becomes slightly acid but is not curdled. Indol is not formed. Dextrose is fermented but no gas is produced. No acid is obtained from lactose fermentation. Invisible growth on potato.	Actively motile with numerous flagella. Indol is not produced. Milk is not curdled. Dextrose is fermented with gas production but no gas or acid is formed from lactose. Distinctly pathogenic for animals and for man.

The agglutination reaction may also be used to differentiate the members of the colon-typhoid group. As a rule, the blood-serum of patients with an acute or chronic typhoid infection will agglutinate and inhibit motility in a hanging drop suspension of B. typhosus, but such a reaction rarely occurs when typhoid serum is used with B. coli, at least in relatively high dilutions. Normal serum may have the power to agglutinate certain strains of bacilli in low dilutions, such as 1:5 to 1:10. There are certain exceptions to the general rule of specific agglutination, which have been mentioned in the chapter dealing with typhoid infection, but for practical purposes such reactive phenomena to the patients' sera have considerable diagnostic importance.

Despite the fact that B. coli is a normal inhabitant of the body, no general immunity reaction, such as that of agglutination, is shown by the blood of normal persons.

Christophers has stated that a large proportion of normal human sera will cause agglutination of B. coli in dilutions varying from 1:20 to 1:200. It would seem if this were universally true that considerable natural immunity was possessed by most individuals toward the organism, which clinically does not seem to be in accord with the facts. In my experience, normal human serum does not possess agglutinins for B. coli. For example, in a recent series of tests, the sera of five individuals did not cause agglutination with loss of motion within one-half hour in dilutions higher than 1:5. On the other hand, the sera of five individuals who had, within one year, received a series of antityphoid vaccinations possessed agglutinins for B. coli within one-half hour in dilution 1:20. The serum of an individual who had typhoid ten years before possessed no agglutinins for B. coli in dilution 1:5, while the serum of one patient with long-standing B. coli bacilluria possessed agglutinins to his homologous strain, following a series of autogenous vaccinations, in dilution 1:20.

On the other hand, when B. coli becomes an inhabitant of the bloodstream or of certain organs, there producing symptoms of inflammation with destruction of tissue cells, a reactive phenomenon to its presence occurs with the development of specific agglutinins. Such agglutination is probably specific only for certain groups of strains, since it is well known that not all strains react alike in this respect.

It is not known upon what the varying susceptibility depends. The reaction is probably more or less a group phenomenon, for it is recognized, as mentioned above, that some strains of B. coli will react positively with typhoid blood-serum. Such reactions are usually not confusing, for, while sera may give non-specific reactions, such reactions occur in comparatively low dilutions, while, in specific reactions to infection, agglutination and paralysis of motility occur in much higher dilutions. For example, in studying the agglutinative powers of a patient's blood-serum toward a strain of organisms isolated from the urine in cystopyelitis, it was found that agglutination occurred in dilution 1:100 in 30 minutes. When the blood-serum was tested against a stock strain of B. typhosus, it was found that agglutination did not occur in dilution 1:20 in one hour, while with a stock strain of B. coli agglutination occurred in dilution 1:80 in 20 minutes. If the cultural characteristics were not too much at variance such evidence would favor B. coli as the causative organism in a suspected infection. In my experience, agglutination in dilution above 1:40 has diagnostic significance.

Other organisms, such as B. enteritidis of Gärtner and B. psittacosis, resemble more or less closely the organisms of the colon-typhoid group and may be found in lesions in the tissues. Thus the B. enteritidis may be associated with B. coli, which may seem to be possessed of exalted virulence, in fatal hemorrhagic gastro-enteritis due to eating putrefied meat. It has been contended by some observers that under such conditions the B. coli becomes highly virulent for man in the intestine. The B. enteritidis closely resembles the paratyphoid organism (see below) in that indol is not produced and the fermentation sugar tests correspond.

The paracolon and paratyphoid groups, first discovered by Achard and Bensaude (1896), more thoroughly studied by Gwyn (1898), Schottmüller (1901), and Buxton (1902), have been frequently encountered in association with lesions produced by members of the colon group. These organisms of themselves may produce ulcerative lesions of Peyer's patches, although very severe forms of gastro-enteritis without ulceration are occasionally encountered in which these organisms seem to play an etiologic rôle. Two types are recognized, A and B. Type B is probably more widely distributed, and is the organism usually present in so-called paratyphoid fever. The types of B. paratyphosus resemble B. coli in that acid and gas are produced in dextrose media, while they resemble B. typhosus in not causing coagulation in litmus milk (Schorer). The close resemblance of the paratyphosus groups to the bacillus of hog cholera (B. choleræ suis), B. enteritidis, the bacillus of mouse typhoid (B. typhi murium), and B. psittacosis, extends even to similarity in agglutination and immunization experiments.

The B. proteus (Hauser, 1885), which has been occasionally found in association with B. coli in abscesses and in gastro-enteritis, can be differentiated, as a rule, without difficulty. This organism, commonly found in decomposing organic matter, apparently has been responsible for certain endemics of food poisoning. It was formerly regarded as the cause of some cases of acute infectious jaundice (Weil's disease). In tuberculous cystitis the secondarily infecting organisms frequently belong to the proteus group, although just why this association occurs, if it is anything more than coincidence, is not known.

TOLERANCE TO B. COLI OF TISSUES OUTSIDE INTESTINAL TRACT

The constant presence of this organism in the lower intestinal tract in man has been mentioned above. Under certain conditions, which are not difficult to conceive because of the proximity of the urethral opening, especially in women, the organism becomes an inhabitant of the urinary tract. In fact, during pregnancy or the puerperium, this organism can be isolated from the urine in about 20 per cent of the cases (Dudgeon). Since its presence does not apparently in the vast majority of puerperal patients produce symptoms or complications, it may be regarded as a normal inhabitant, under certain conditions, of the urinary tract.

That the organism in these instances does not produce symptoms or complications when located in the urinary tract depends upon such factors as (1) virulence of the organism, (2) local cellular resistance or immunity, (3) absence of tissue lacerations or abrasions through which the organism may reach deeper structures.

The first factor, the virulence of the organism, may depend upon the amount of putrefactive disturbance in the intestinal tract giving origin to the infection. Many writers are convinced that B. coli isolated from an intestinal tract in which stasis and putrefaction are present, as evidenced by indicanuria, is more virulent. Symbiosis may enter into the question of virulence and tissue resistance. For example, the association of B. coli and B. typhosus or the toxic products of either accentuate the virulence of the other. Guinea pigs and rabbits, which may resist the subcutaneous dose of a culture of B. typhosus, quickly die of a generalized infection if a sterile culture of B. coli is injected into the peritoneal cavity. The special susceptibility of tissues may also influence virulence. B. coli isolated from a septic peritonitis is as a rule much more virulent for animals than the strain isolated from the intestinal tract of the same individual.

Of local cellular immunity little is known, although it is recognized that the cells of certain tissues may show greater resistance to certain infections than the cells of other tissues. For example, the pneumococcus is seldom isolated from ordinary furuncles or skin abscesses, nor does it produce lesions of the mucous membrane of the mouth, although it is normally present there in a large proportion of individuals during the winter months. Nor does the B. coli commonly produce furuncles or skin abscesses, even though an abrasion is present, although most individuals come in daily contact in one way or another with the organism.

Of the third factor it may be granted that absence of tissue laceration must prevent, in most instances, spread of the infection to neighboring lymphatics, the blood-stream, and distant tissues. On the other hand, when laceration of tissue, even though microscopical in extent, has occurred during pregnancy, or the trauma incidental to surgical procedures, the avenue of entrance is established. The experiments of Heinricius, which consisted in the injection of bouillon cultures of B. coli into the uteri and vaginæ of rabbits, showed that the intact epithelium prevented infection of the underlying connective tissues. Where the epithelium had been abraded the tissues beneath the epithelium were swarming with organisms. He found that in general there was some similarity between the action of B. coli and streptococci in producing a bacteriemia. Some differences could be seen, however. The B. coli seemed to infiltrate the connective tissues in all directions, disregarding the lymph channels, while the streptococci followed the lymph channels.

SPREAD OF INFECTION TO OTHER TISSUES

The textbooks of a decade ago referred constantly to an ascending infection of the urinary tract, by which it was intended to imply that infective organisms entered the urethra and by continuity of tissue traveled upward to the bladder and then in many instances to the pelvis of the kidney. It has been practically decided by most authorities that an ascending cystopyelitis is rare. The organisms much more commonly reach the kidney pelvis by way of the lymphatics or blood-stream or by continuity of tissue from the colon. Rolleston believes the transperitoneal method of infection from the colon to the kidney by way of the lymphatics to be common. Franke's experiments seemed to show that the ascending colon and cecum were connected by lymphatics with the right kidney, but he was unable to find such a connection between the colon and the left kidney. This work needs confirmation. Rovsing believes in the spread of the infection to the kidneys by the hematogenous route. He had treated, up to 1909, 285 patients with B. coli infections, and in 180 of these the disease arose as an acute nephritis. In no instance had the patients been catheterized.

On the other hand, because of the more or less constant presence of bacteria including B. coli in the vagina, it is not difficult to understand the manner by which they reach the bladder through the short urethra of women and children. Their presence there does not necessarily mean an inflammatory reaction and cystitis. In my experience, however, B. coli has been found more frequently in cystitis than any other organism. It has been found frequently in association with the tubercle bacillus in tuberculosis of the kidney and bladder. Likewise it is the organism frequently found in the urine when calculi are present in the pelvis of the kidney, ureter, or bladder. Ohlmacher has recently reported the presence of B. coli in five out of eight instances of bacteriuria associated with urinary calculi. The more or less frequent presence of B. coli in leukorrheal secretions would seem in some instances to be a possible cause of sterility, since an excessively acid secretion would inhibit the activity of, if it did not kill, spermatozoa. This fact has been emphasized by Morris. Considering the apparent ease with which an infection by B. coli can reach the uterine cavity and tubes from the vagina, it is somewhat surprising that this organism is relatively so infrequently encountered as the causative factor in ovarian abscess and tubal infections. Grover has recently described fatal peritonitis due to B. coli which followed perforation of the uterus in a probable attempt to produce abortion. Peritonitis following perforative appendicitis and subphrenic or liver abscesses following cholecystitis are frequently due to B. coli.

An attack of pelvic peritonitis may follow infection with B. coli from the vagina by ascent through the uterus without, so far as the patient is concerned, provocative cause. In fact, lacerations of the hymen serve as the entering point of infection to the bladder, kidney pelvis, and peritoneum through the lymphatics in more instances than are generally recorded. Such a sequence in a recently married woman is commonly ascribed to the organism associated with specific urethritis. Wildbolz has recently described infection of the bladder and kidney pelvis in eight such cases by B. coli. Murray, Williams, and Wallace found B. coli present in 44.5 per cent of gynecologic cases with normal urine prior to operation and in 93 per cent subsequent to operation. There appeared to be no relation between postoperative temperatures and the presence of the bacillus in the urine.

SYMPTOMS OF INVASION OF GENITO-URINARY TRACT BY B. COLI

Urethritis.—Normally in healthy women or men the urethra is uncontaminated, but if any damage has previously been done to the lining membrane by trauma incident to childbearing, by the forceful passage of a sound, by infection from an unclean catheter, by gonococcus infection, or as the result of irritation due to the constant passage of infection from above, such as tubercle bacilli from an infected kidney or bladder, then and subsequently contaminating organisms are frequently present in the urethra. The two most common organisms found in non-specific urethritis are the Staphylococcus albus urethræ and B. coli. In fact, these organisms may be present in the urine with no urethral symptoms. Dudgeon has stated that he has never seen an acute B. coli urethritis in men. Scherck's experience has been similar. Kolle, on the other hand, found B. coli as a secondary infection in 6 out of 12 cases of urethritis. Chronic gonorrheal urethritis is often prolonged by the presence of B. coli. Reynolds has emphasized the importance of the B. coli in the production of epididymitis secondary to chronic gonorrheal posterior urethritis.

Cystitis.—In simple primary cystitis due to B. coli the symptoms are usually not severe, but point, as a rule, to local involvement of the posterior urethra and bladder. In males the prostate gland and seminal vesicles may be involved. The symptoms are frequent desire to empty the bladder and a burning or scalding sensation along the urethra, associated with the passage of small quantities of acid, turbid urine. Examination discloses, as a rule, some tenderness in the rectum, and in males the prostate gland may be swollen and tender. In women leukorrhea may be present. The urine contains many polymorphonuclear leukocytes, as a rule, although pus may be absent and the turbidity be due to the large numbers of bacilli suspended in it. The acidity is usually much increased, varying from 600 to 800 per 1,000 in terms of decinormal sodium hydrate. Cultures taken from urine secured under aseptic precautions upon nutrient agar disclose a rapidly growing, slowly motile rod, which conforms to the cultural characteristics mentioned above. The most important of these characteristics are acid production and curdling of milk, the production of indol, gas production in gelatin stab, and fermentation of dextrose and lactose with acid production. The organisms grow and reproduce rapidly at room temperature, although at 37° C. their reproduction is most rapid. Barber found the generation rate to be seventeen minutes at 37° C.

If the urine to be examined culturally is secured from a female, the specimen should be secured in a sterile glass through a sterile catheter and after thorough cleansing of the urethral orifice. As ordinarily performed, it has always been a wonder to the writer why more infections of the bladder do not occur following catheterization, since the B. coli so commonly contaminates the pubic region and the urethral orifice. Such bacteria on the surface are introduced regardless of the care used. The urethral orifice should be cleansed with a mercury bichlorid or phenol solution. The first portion of urine passed should be discarded and the remaining portion collected in a sterile glass, from which the culture should be taken. Acute cystitis in children has, in my experience, frequently been due to B. coli. If fever is present, it speaks for involvement or extension of the infection elsewhere, most commonly pyelitis, to the pelvic peritoneum or ovaries, the prostate gland or seminal vesicles. Ulcerative lesions in the bladder due to B. coli are rarely seen in acute cystitis, but may occur in chronic forms associated with stone and sacculation. Non-specific prostatitis (often due to B. coli) is more common than is generally recognized, especially in individuals past mid-life.

Pyelitis.—According to Billings, the B. coli is found as the infective organism in about 50 per cent of all cases of bacteriuria. Lenhartz, however, found B. coli alone in 66 out of 80 patients with pyelitis (75 per cent). The infection may reach the kidney pelvis by ascension from urethra and bladder (urogenic), by the blood-stream (hematogenic), from the intestine (transperitoneal), or by way of lymphatics from some focus of infection in the neighboring tissues. A vast majority of instances occur in women; thus Lenhartz found 74 instances in women out of 80 primary pyelitis cases; most instances occurred after pregnancy or childbed. Malformation or displacement of the kidneys seems to predispose to infection. The right kidney is much more frequently affected than the left. In 65 out of 70 cases (93 per cent) the right kidney was involved, according to the experience of Legueu. The acute onset is usually severe, with rigor and fever from 101° to 104° F. Tenderness may be present by palpation over both kidneys at the costovertebral angles (Brewer's point), although the tenderness is usually more marked over one side. The spleen is usually palpable. A leukocytosis of from 12,000 to 25,000 is usually present. There is constant desire to void urine, which is turbid from pus and bacteria and acid in reaction. The urine is, as a rule, voided painlessly.

A majority of the instances of kidney involvement follow operative procedures. Fenwick has described the frequency of pyelitis following operations for hemorrhoids, which he has ascribed to the following causes: (1) surface lesions in an infected area; (2) congestion of the vesical neck; (3) retention of urine.

The infection may reach the kidney pelvis through extension along the periureteral lymphatics. Sugimura has described the conditions found in twenty-five patients with cystitis. He believes that, although the urethral orifices may be reddened and apparently involved, extension upward of the infection occurred in all by way of the lymphatics and not by ascension through the ureters. The fact that many instances of postoperative kidney infection occur in which there has never been an antecedent cystitis or catheterism lends support to the view of extension by way of the lymphatics or blood-vessels.

Perhaps the most important single predisposing factor leading to localization of infection in the kidneys, aside from contiguity of infected tissue, is found in the ureters where strictures and kinks, many times associated with kidney ptosis, are more common than generally believed. Such conditions may produce but few symptoms of vague character, such as lumbar backache, while quiescent and while the obstruction is partial in nature. The trauma incident to operative procedures, especially about the appendix and in the pelvis, serves, in the presence of such oftentimes unrecognized predisposing conditions, to explain the subsequent infection of the kidney structure which follows. Cystoscopy, ureteral catheterism and the pyelogram are important aids and should be more generally employed, since the information obtained can be secured by no other means. Under conditions such as stricture or kink in the ureter the colon bacillus seems to have a predilection for the upper urinary tract.

Furniss believes the late occurrence after operation lends weight to the belief that the origin of the infection is from thrombi at the site of operation. While the symptoms are usually suggestive of kidney involvement, such an infection may be mistaken for other acute conditions, such as appendicitis, peritonitis, cholecystitis, pelvic vein thrombosis, prostatic abscess, seminal vesiculitis, or an ether nephritis. A true infectious nephritis usually accompanies the pyelitis. In fact, in most instances, the infection by way of the blood-stream reaches the kidney pelvis through the kidney parenchyma. The only exceptions would appear to be those in which the infection reaches the kidney pelvis by extension upward along the periureteral lymphatics or by ascension through the ureter in rare cases. Localization of the infection in the parenchyma with miliary abscess formation may accompany the pyelitis. As has been pointed out by Rovsing, the small miliary abscesses closely resemble macroscopically the miliary tubercles present in tuberculosis.

The acute stage of pyelitis, with continuous or remittent high fever, perhaps with recurring chills, although more commonly a single initial chill occurs, lasts usually from one to three weeks. Hematuria occurs more or less frequently as an initial symptom, and is soon followed by albuminuria, pyuria, and bacilluria. Casts are not usually found in pyelitis, a point emphasized by Abt and Wassermann, but are present in pyelonephritis. The fever disappears, in some instances by crisis, although in probably three-fourths of the cases the fever gradually becomes remittent and disappears by lysis. With the disappearance of the fever the urinary findings may improve; that is, the amount of pus may diminish and there may be a decrease in the number of bacilli, but, as a rule, there is no essential change in the bacilluria. After an afebrile period of from three to ten days a relapse may occur or a new attack involving the hitherto intact kidney pelvis may take place. In fact, febrile disturbances may alternate with afebrile intervals over a considerable time until the process becomes chronic, or the pyuria and bacteriuria may become chronic without marked local symptoms, such as dysuria or pain. If obstruction to the free flow of urine has occurred, as a result of calculi, prostatic swelling, sacculation or atony of the bladder, ureteral kink, or pressure obstruction, symptoms such as fever and rigors promptly follow. It is surprising, however, what large quantities of pus may be eliminated in chronic infections involving the kidney pelves over periods of months without great apparent harm to the kidney structure. In many instances the pyuria and bacteriuria continue for months, and, aside from some loss of weight, strength, and appetite, with the development of pallor due to secondary anemia, there are few subjective or objective symptoms.

Thomson believes that the commonest occasion of acute septic invasion of the kidneys by B. coli is in the course of typhoid fever. Chronic ulcerative colitis is another common antecedent. The onset during typhoid is sometimes marked by severe rigors. Their occurrence during the course of typhoid fever should raise the suspicion of acute septic invasion of the kidneys by B. coli. The temperature usually becomes irregular and the quantity of urine diminished. Coleman and Hastings have emphasized the fact that some strains of B. coli are capable of producing a generalized infection clinically identical with typhoid fever. The occurrence of an acute infectious nephritis due to B. coli becomes immediately a serious condition if the patient has previously had evidences of chronic interstitial changes involving the kidneys. In such conditions the invasion may be preceded by an attack of colitis, acute appendicitis, or gastro-enteritis. The urine then becomes decreased in quantity with a tendency to suppression. The presence of fever and an initial rigor frequently lead to a suspicion of pneumonia. Delirium is usually rapidly followed by coma and hyperpyrexia. An acute infectious nephritis due to B. coli terminates a chronic interstitial or diffuse nephritis more commonly than textbooks and recent literature would lead one to suppose. I have seen a number of such instances of sudden onset with enormous numbers of B. coli in the urine.

Acute infectious pyelonephritis due to B. coli may occur during the course of measles, diphtheria, and scarlatina. In such instances, especially in children, the symptoms such as vomiting and abdominal distention may present the picture of an "acute surgical abdomen," and appendicitis, intestinal obstruction, volvulus, or mesenteric thrombus may be suspected. The symptoms may, on the other hand, present the picture of a generalized infection with little pain or tenderness in the kidney region, and as such simulate influenza, typhoid fever, or septic endocarditis. In children and chlorotic girls, because of recurring mild febrile attacks, tuberculosis or chronic tonsillar infection is often suspected. Typhoid fever with an onset resembling an acute nephritis may be differentiated by blood cultures. Because of the recent widespread use of antityphoid prophylactic inoculations, which lead in many instances to persistent blood agglutinins, the Widal reaction will not be as dependable in differentiating infections due to the typhoid bacillus as in former years. Blood cultures should be the diagnostic method of choice.

In pyelitis occurring during pregnancy the B. coli is frequently found to be the causative organism. It is surprising how serious the condition of the patient may appear to be and recovery take place. If the only symptoms are moderate fever, pyuria, and albuminuria without suppression, the patient will usually weather the storm until confinement, even though enormous quantities of pus are present in the urine. When, however, partial suppression occurs, due to the infectious nephritis and stagnation of urine in the kidney pelves, with chills and high fever, the question of artificial delivery to relieve the retention becomes paramount. If the patient has but a few weeks to full term and the infectious process has not existed long enough to produce the appearance of sepsis, with secondary anemia, vomiting, and general malnutrition, it may be wise to wait in order to obtain added security for the fetus. When partial or complete suppression occurs in long-standing infections of this character, if not quickly relieved, it becomes necessary to resort to artificial delivery in order to relieve the retention and save the patient, even though the child be sacrificed. In a few instances, in my experience, vaccine therapy has been of decided value, but these were of the type without suppression (see below). The vaccines seemed to control the fever, without which the condition of the patient's nutrition improved to such an extent that it was possible to await full-term delivery, even though enormous quantities of pus were present in the urine.

DIFFERENTIAL DIAGNOSIS

The diagnosis of uncomplicated chronic B. coli pyelitis or pyelonephritis will depend upon the isolation of B. coli from the urine and the exclusion of other organisms which may produce similar symptoms, such as the staphylococcus, streptococcus, or B. proteus.

The staphylococcus may produce pyelitis or pyelonephritis identical, so far as the clinical picture is concerned, with infection by B. coli. The chronic form of such infections, or infection with B. proteus, produces symptoms of severe intoxication. The more or less constant fever, sallow appearance, history of considerable loss of weight, headaches with loss of strength and appetite often cause a suspicion of typhoid fever. The presence of pyuria, with more or less albuminuria in the filtered specimen, the ready cultivation of staphylococci or B. proteus upon agar, together with a leukocytosis from 12,000 to 20,000 per c. mm. and negative typhoid blood cultures, usually promptly clear up the diagnosis. The presence of stone is frequently suspected, and with justification, even though no attacks of colic or hematuria have occurred. Roentgen-ray examinations are an important aid.

Staphylococcus and streptococcus infections of the kidney structure more frequently follow an angina or scarlatina, or some acute infective process, such as glandular suppuration, peritonsillar abscess, carbuncles, or osteomyelitis than infection with B. coli. B. proteus, as has been mentioned above, is more frequently found in association with the tubercle bacillus in tuberculous nephritis. Staphylococci and streptococci in urine have the power to decompose urea. Such specimens have a strong ammoniacal odor and are alkaline in reaction. Since the bacteria are nonmotile, they settle to the bottom of the container along with pus cells, crystals, and epithelial cells, leaving the supernatant urine clear. The B. proteus likewise has the power to decompose urea. Such urine has a strong ammoniacal odor, and is alkaline in reaction, but since the B. proteus is actively motile the organisms do not settle to the bottom of the container upon standing, and the specimen remains turbid. B. coli infection produces an acid urine which remains turbid upon standing because of the active motility of the organism. Infection by B. proteus can usually be differentiated from infection by B. coli by finding, as has been pointed out by Rovsing, abundant crystals of triple phosphate due to the presence of urea decomposition. The presence of the tubercle bacillus can usually be determined by drying the sediment secured from centrifugated urine upon a glass slide and employing appropriate stains. The bacilli when present occur in small groups. The possibility of confusion with smegma bacilli should be borne in mind, but these can be differentiated by submerging the slide in weakly acidulated alcohol, which decolorizes the smegma bacillus.

Other Lesions Produced by B. Coli.—Chronic gonorrheal urethritis may be prolonged by the B. coli as a secondary infection, which reaches the urethra through unclean instrumentation by the physician or unclean urethral syringes so frequently used by the patient. The infection may reach the posterior urethra and prostate, and by extension through the ejaculatory ducts involve the epididymis. Reynolds has recently emphasized the occurrence of epididymitis due to B. coli. Von Schrötter and Weinberger have observed B. coli in the sputum of a patient with a long-standing bronchopneumonia. Pearson has reported B. coli in the cerebrospinal fluid of a fatal case of meningitis, which apparently followed suppurative otitis media. Hartwich also found B. coli in the cerebrospinal fluid of a patient with tuberculous ulceration of the intestine. W. S. Stone believes B. coli to be responsible for a few fatal generalized infections during the puerperium. I have never personally seen such an instance.

TREATMENT OF CYSTITIS AND PYELITIS DUE TO B. COLI

Cystitis.—The use of an autogenous B. coli vaccine in cystitis due to this organism, without infection higher up in the tract, has been followed by good results in my hands in numerous instances. The condition seems to be most common in women with relaxed vesicovaginal walls following the trauma of childbirth. Salol, gr. 30 to 45 (2.0 to 3.0 gm.), daily in adults with large quantities of distilled water (3 quarts daily) has been used as an aid to the vaccine treatment. Hexamethylenamin, gr. 10 (0.65 gm.), with acid sodium phosphate, gr. 30 (2.0 gm.), three or four times daily, while apparently efficient in bladder irritation due to B. typhosus, has not been followed by such satisfactory results in the treatment of B. coli cystitis. Hexamethylenamin may cause renal and vesical irritation if used for long periods. It may also cause reduction of Fehling's solution, simulating a sugar reaction. This has also been Rolleston's experience. The dosage of vaccine which has seemed most efficient has been 50,000,000 to 100,000,000 at four to five-day intervals. Preference, in my experience, should be given to the use of the so-called sensitized vaccines ("sensitized bacterins") in this condition, since larger doses may be employed with less local and general reactions. Mercurochrome may be used in 1 to 2 per cent solution for bladder instillation in the treatment of cystitis. The organic silver preparations, such as argyrol, silver nucleinate, or silver iodid in the form of a 5 per cent emulsion in acacia, are also useful.

Pyelitis.—The acute symptoms of uncomplicated pyelitis usually promptly subside when rational treatment is instituted. This should consist of rest in bed, a liquid diet, large quantities of water, distilled preferred, and salol or hexamethylenamin internally, 45 to 60 gr. (3.0 to 4.0 gm.), daily. The so-called alkaline treatment of citrate of potash or soda bicarbonate is preferred by some clinicians. The bacilluria may, however, persist, and because of recurring acute exacerbations the condition becomes chronic, despite the treatment. In such instances the patients present a sallow cachetic appearance, periodic fever exacerbations occur, hematuria may recur, and malignancy, tuberculous nephritis, and stone are frequently suspected.

Drainage of the kidney pelvis by means of the ureteral catheter followed by instillations of 3 to 5 per cent solutions of silver nitrate will be followed by marked improvement in many patients, especially if but one kidney is involved. Possibly one-third of the patients will be cured, one-third improved, while one-third will obtain no relief.

If the pyelitis is complicated by conditions which interfere with free drainage and thus favor retention, such as ureteral kinks or stone, prostatic hypertrophy, stricture, atony of the bladder, or pressure arising from uterine or ovarian neoplasm, little may be expected of any treatment except amelioration of symptoms until such conditions are corrected.

Vaccine therapy should be tried in all cases of chronic uncomplicated pyelitis. Cabot found that improvement in clinical symptoms occurred in about 50 per cent of the cases of chronic B. coli bacilluria treated by vaccines. Geraghty, on the other hand, found no improvement which could be attributed to vaccine therapy in the treatment of urinary tract infections. Scherck has also found vaccine therapy with both stock and autogenous strains of little service. On the other hand, the results occasionally obtained warrant the trial of vaccine therapy in any condition not amenable to other measures. Such an instance among others within my experience may be cited.

At about the fifth month of pregnancy this patient began to pass large quantities of pus and blood with the urine. The daily temperature ranged from 101° to 103° F., with occasional chills. This condition was not amenable to any form of treatment during one month by the attending physician. At this time cultures taken from the urine showed B. coli in pure culture. The patient presented a sallow cachectic appearance, while the vomiting and malnutrition incident to the febrile disturbance made the outlook unfavorable to the completion of term. An autogenous vaccine was prepared from the cultures. After the second dose of 50,000,000, the temperature dropped abruptly by crisis to normal and there remained. In all ten or twelve injections were given, and, although the pyuria and bacilluria did not disappear until after the retention was relieved at term, her general condition improved with the disappearance of the fever, and she was delivered of a healthy child. Her complete recovery followed.

Hicks has reported the successful use of B. coli vaccine in the treatment of a patient with pyelitis of pregnancy. As in the case cited above, the fever, which had been more or less constant, dropped almost immediately after the first inoculation, and remained normal thereafter. The pain also rapidly subsided, and the patient's general condition improved. The pyuria persisted for some time and was intermittent in character. Billings believes vaccine therapy of decided value in the treatment of B. coli infection of the urinary tract. Spontaneous abortion has been mentioned by Billings and Irons as having occurred in two patients with pyelitis, in the third and fourth months of pregnancy respectively, following the inoculation of moderate doses of colon vaccine. As stated by them the relation of the abortion to the inoculations may have been coincidental.

If an autogenous vaccine is to be used it should be recalled that some strains of B. coli cause relatively severe local and general reactions. It is therefore wiser, until the toxicity of the strain has been determined by clinical trial, to start with relatively small doses of 25,000,000 to 30,000,000. Some of the strains produce less reaction in doses from 100,000,000 to 200,000,000 than others in doses of 25,000,000.

It is possible to render an autogenous vaccine less toxic by suspending the bacterial cells, after standardization, in salt solution for forty to forty-eight hours at 37° C. in the incubator. Autolysis takes place and the salt solution becomes toxic. The cells are thrown down by centrifugation, the toxic salt solution discarded, and the bacterial cells resuspended in fresh salt solution containing 0.35 per cent phenol. In my experience the best results have been obtained by gradually increasing the dosage, depending upon signs of local and general reaction, from 25,000,000 to 200,000,000 at four to five-day intervals.

In chronic uncomplicated pyelitis due to B. coli, if satisfactory results are not obtained through the combination of salol with the copious ingestion of water and the use of an autogenous vaccine, it may be necessary to resort to the method of continuous drainage, the "catheter à demeure," as advocated by Rovsing in 1897. This consists in putting the patient to bed and securing continuous drainage by means of a Mercier's formalin-sterilized rubber catheter in the bladder, in addition to the treatment outlined above. The formalin sterilization hardens the rubber, and it may remain in the bladder for from three to four weeks without change. When cultures show that the catheter may be removed Rovsing recommends, immediately prior to removal, the injection of 50 c.c. of 1 per cent solution of silver nitrate in order to rid the bladder of any bacilli concealed in the vesical folds. For women Rovsing recommends a Pezzer's catheter, No. 22 or 23, which is easily kept in place.

This treatment is founded upon the fact that continuous drainage is necessary in chronic pyelitis or pyelonephritis to rid the tissues of bacilli through the urine, since the time which may elapse between urinations is sufficient for the development of enormous numbers of bacilli. Reinfection of the upper urinary tract may thus constantly occur through the lymphatics from the connective tissue of the bladder. As has been mentioned above, Barber found the generation time of the B. coli to be seventeen minutes at body temperature. The only difficulty encountered is to secure enough time to complete the cure, since many patients object to a period of three to four weeks in bed.

TREATMENT OF INFECTED WOUNDS BY B. COLI VACCINES

In about twenty-five infections of the drainage tract following appendicitis and cholecystitis due to B. coli, treated by autogenous vaccines, the results have been satisfactory. The patients were discharged in shorter time than was possible in patients not so treated, due to the lessened fever and wound discharge following the bacterial inoculations. There were also fewer complications during the course of vaccine treatment. In a few patients the discharge ceased after two or three inoculations.

Hoobler has reported the use of B. coli vaccine in a patient following evacuation of a pelvic abscess. The dosage was gradually increased, twice weekly, from 25,000,000 to 200,000,000. In all thirteen inoculations were given. The patient made a slow but complete recovery. Stoner, in his résumé of vaccine therapy, mentions three patients operated on for cholecystitis with gall-stones, in which B. coli infection complicated the recovery. The vaccine inoculations seemed of value in all.

Vaccines sensitized by the addition of an immune serum and subsequently killed produce less constitutional reaction when injected and should generally be preferred for this reason. This immunizing response has apparently been fully as great as that produced by vaccines made from autogenous strains. Much more rapid absorption of the vaccine occurs after an intramuscular injection than occurs after a subcutaneous injection and should usually be the method of choice.

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CHAPTER XIV

PSITTACOSIS

ALLAN RAMSEY

REVISED BY GEORGE BLUMER

Prophylaxis.—The general facts connected with the etiology of this disease furnish us with the clues to prophylaxis. In 1879 and 1882 there were reports of small epidemics of a severe atypical pneumonia which was ascribed to contagion from parrots. Shortly before the development of these cases it was found that parrots had died of some acute disease in the various homes of all these patients. Many other epidemics of this disease, now known as psittacosis, were subsequently reported, and the parrot was invariably considered as the source of the infection.

In December, 1891, 500 parrots were shipped from Brazil to the Paris market. During the voyage 300 of these died and the remaining 200 reached Paris in February, 1892. During that year 49 cases of psittacosis developed throughout the city, all being ascribed to these parrots.

In Florence in 1894, in a family in which a parrot had just died, there developed 5 cases, 3 of which were fatal. In 1898 in the Julian Venetia 3 cases developed in a house where 2 parrots had died shortly before.

In 1898 house epidemics in Cologne were reported by Leichtenstern.

Without going into the details of the bacteriology of this disease, suffice it to say that in only one instance has an organism been isolated from a human being with psittacosis. In this case (Gilbert and Fournier, 1896) the organism belonged to the typhoid-colon group and appeared to be the same as Nocard's organism obtained from parrots. In 1893 Nocard isolated a bacillus belonging to the colon group, and he regarded it as specific, but examinations by others of both parrots and human beings who have died of psittacosis have usually failed to show this organism.

In fact, the exact relationship between the disease of the parrot and the illness of the people in the same house has not as yet been determined. Warthin states that "the bacteriology of psittacosis and the true relations of the parrot disease to the atypical pneumonia seen in man are yet to be definitely determined." Although he could not absolutely prove it, Leichtenstern believed that the cases reported by himself were due to infection from parrots.

A glance at the parrot business will prove instructive and will throw light upon both the dissemination and prevention of psittacosis. The business is a large one, and thousands of parrots are brought annually, especially to the markets of Italy, Germany and Paris.

One firm advertises that it actually imports 80,000 of these birds annually. The death-rate among them, however, is enormous, and within six weeks of their importation large numbers of them die. Of 500 purchased in Brazil for the Paris market, 300 perished during the voyage, and in all probability many of the remaining 200 died shortly afterward in the parrot emporiums of the city.

The cause of this high mortality lies probably very largely in the filthy and unsanitary conditions under which the parrots are kept when they are brought into captivity. They are taken from a state of perfect health and transported in a badly ventilated vessel; their cages become soiled with their own excreta, and in a short time are in a filthy state. Enforced captivity under these conditions kills many of them while on the ship. But these conditions continue in a great measure in the city emporiums, so that within five or six weeks after their importation very many more of the birds have died. What the specific virus that kills them is, as has already been stated, still unknown. The infection may originally have been confined to the ships, but it has now become endemic in the various places where the parrots are landed. Many healthy birds that are brought to the shops and emporiums soon become infected and die.

Under natural conditions the parrot is a hardy bird, and some varieties of it live to the remarkable age of seventy and even ninety years. Moreover, they thrive in captivity when they are well taken care of, and when rationally treated they will live even in confinement for fifty or seventy years.

It is, then, under conditions of filthy cages and bad hygiene that the high mortality of imported parrots occurs. In view of these facts, it would seem that cleanliness and good hygiene should be the basis of prophylaxis. All cages should be kept clean and the infected ones should be steamed or scalded, as an ordinary cleaning will not destroy the virus. The dead parrots should be burned. Periodic government inspection of all shops and emporiums where parrots are sold has been advocated, so that dirty or infected shops might be closed until they were cleaned or disinfected. This government inspection has probably not been adopted yet by any city or country.

In 1897 an outbreak of 14 cases occurred in Genoa and a few in Florence. Believing that the parrots were the source of the disease, the Genoese Town Council, acting upon the advice of their medical adviser, issued a circular prohibiting the keeping of parrots in private houses.

In the province of Undine similar measures were adopted. This is interesting as showing a rational attempt at prevention, but, as the outbreak in Genoa comprised only 8 cases, and as other outbreaks or epidemics have always been small, it is impossible to draw any conclusions as to the prophylactic value of the edict of the Genoese council.

Treatment.—This is purely symptomatic. The disease has a bad prognosis, as the mortality is about 35 to 40 per cent. The probabilities are then, that, in view of this high mortality, symptomatic treatment accomplishes but little.

The patient should be placed in a well-ventilated room, and, in the present state of our knowledge upon the subject, it is best to isolate him. A liquid diet should be instituted and maintained throughout the period of anorexia and high temperature. As soon as the fever declines and the state of the digestive organs will permit, the diet should be somewhat increased, as many patients are very weak, and their strength should be kept up as much as possible by a nutritious diet.

In those cases in which constipation is present an initial purge should be employed, after which use may be made of an enema. In many cases it is probably well to use a purge again once or twice in the course of the disease.

For high temperatures cold sponging may be employed; usually, however, high temperatures are of short duration and seldom require any vigorous treatment.

The actual treatment of this disease is purely symptomatic, and there are no drugs that influence its course or duration. Internal medication is chiefly stimulation, for which any of the stimulants may be used. The infection is generally a severe one, and sooner or later supporting measures are indicated in a great many of the cases. I know of no cases in which the cold, fresh-air treatment has been tried, as in ordinary lobar pneumonia. As the pneumonia of psittacosis is usually lobular, the fresh-air treatment would probably accomplish nothing.

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CHAPTER XV

ACUTE BACILLARY DYSENTERY AND BACILLARY DYSENTERY IN CHILDREN

Charles Warren Duval, Isaac Ivan Lemann and Wilburt C. Davison

Definition.—Bacillary dysentery is an acute infectious disease caused by a specific bacillus, and characterized by an acute inflammatory process of the intestinal mucous membrane, more especially that of the large gut. The disease may be divided into: (1) the epidemic form which is caused by the true Shiga bacillus; and (2) the sporadic or endemic type which is due to some one of the paradysentery bacilli.

Although bacillary dysentery is an extremely prevalent disease, occurring in epidemic form in the tropical and temporate zones and appearing endemically throughout the world, its etiology was obscure until 1898 when Shiga determined, with scientific accuracy, the causal agent in the acute epidemic variety. The etiological importance of Shiga's discovery has been thoroughly exemplified by many investigators in all parts of the civilized world. Flexner and his coworkers are largely responsible for our present knowledge of the etiology of bacillary dysentery other than the epidemic form. The investigations of Duval and Bassett in the summer of 1902 demonstrated an etiological relationship between a specific bacillus (paradysentery) and infantile summer diarrhea.

Since the determination of the causal agent in the various forms of acute dysenteries has an important bearing upon serum or vaccine treatment, it is well to discuss briefly this question of varieties of the dysentery organism, and state in the opinion of the writers their possible significance. Although many varieties of dysentery bacilli have been described and regarded by those reporting them as strains of the same species, the status to-day is that acute bacillary dysentery is caused by two distinct bacterial species.

In 1903 it was established that two distinct types of bacilli occur in dysenteric stools, the true Shiga type and the type that ferments mannite, which has subsequently become known as the Flexner stem or paradysentery bacillus, of which there are a number of strains. The Shiga bacillus is responsible for the epidemic dysentery and the Flexner stem for endemic and sporadic dysentery.

Kruse was the first to show that the dysentery bacillus of Flexner and that isolated from the asylum dysenteries, though alike in respect to each other, differed in agglutinability and pathogenicity from the Shiga bacillus of epidemic dysentery and therefore constituted a distinct species. Subsequently many investigators have not only confirmed this distinction, but have established other important and constant differences, which further separate the Shiga and Flexner bacilli. It is noteworthy that the Shiga bacillus is rarely met with outside of epidemics, while the paradysentery group of which the Flexner bacillus is representative is of widespread distribution and possibly a normal inhabitant of the intestinal tract (Duval). This would account for the fact that the Flexner bacillus occurs in the stools of the epidemic dysentery, and in a large percentage of cases as the epidemic wanes, playing the rôle of a secondary invader.

Terminal dysentery is a frequent occurrence in a great number of diseases, and in the experience of the writers it is the Flexner organism that occupies the clinical field at death. In hundreds of such cases examined bacteriologically by one of us (Duval) the Shiga bacillus has not been encountered, consequently we can state that the Shiga bacillus is rarely met with in sporadic cases of dysentery, and never plays the rôle of terminal invader. Furthermore, in addition to distinct cultural and agglutinating differences, Flexner and Sweet have shown that the Shiga bacillus produces a soluble toxin while the toxic substance of the Flexner organism is intimately bound up in the bacterial cell. While many American observers are generally inclined to consider the Shiga and Flexner organisms of similar etiological importance, the Germans, who regard the difference between the organisms as significant, consider the Shiga type as the only one which has a causal relationship to acute epidemic dysentery. That the two organisms both produce acute inflammation of the gut characterized by the same general symptom-complex is no reason for thinking that they are not different species since the various parasitic intestinal bacteria closely resemble one another. Thus the typhoid and paratyphoid bacilli are distinguished by methods not more definite than those differentiating the Shiga and Flexner bacilli. On the basis of so many essential distinctions, and in spite of the similarity in morphology and cultural properties, we may conclude that the bacillus of sporadic, endemic, institutional dysentery and the summer diarrheas of infants (the paradysentery group or mannite fermenters) is not related specially to the Shiga organism.

Pathology.—The essential lesion of bacillary dysentery is in the intestinal tract, almost invariably of the large gut, and primarily at the various flexures. In severe cases the lower portion of the ileum, together with the large intestine, is the seat of pathological change. Occasionally the lesions have been noted throughout the whole of the small intestines, extending as far as the pyloric orifice.

In general the mucosa and submucosa of the intestine are swollen, edematous, and dark red in color, and not infrequently covered entirely or in part with a fibrinous exudate (pseudodiphtheritic membrane). Blood-streaked mucus may be found in considerable quantities associated with the exudate or in the gut content. There may be, however, an absence of membrane, the mucosa showing merely discrete and confluent ulcers or shallow erosions, which rarely extend below the muscularis mucosa. Fatal acute hemorrhage is exceedingly rare and perforation of the gut with peritonitis is almost unknown in uncomplicated cases of bacillary dysentery. One of us (Duval) has seen a case where the dysenteric ulcer perforated and gave rise to a fatal peritonitis. This was a sporadic case of dysentery due to the Flexner bacillus which occurred at the Touro Infirmary in 1911. Diphtheritic membrane on the vagina and on the cervix and edema of the abdominal wall has been observed (Lemann) in another case of sporadic dysentery. The Shiga bacillus was recovered from cultures taken from the vagina.

The mesenteric lymph-nodes are occasionally enlarged, due presumably to the absorption of the specific toxin, or, what is more likely, the result of invasion of other microörganisms from the intestinal tract. It is noteworthy in this connection that B. dysenteriæ has never been recovered in pure culture from the enlarged mesenteric glands. In these cases the specific organism is always associated with colon bacilli and other allied species.

Bacillary dysentery, unlike typhoid, rarely gives rise to a bacteriemia; the organism remains throughout the course of the disease at the site of the initial lesion. It may enter the circulation from time to time, but is quickly killed out, proof of which are the negative blood culture findings. Recently, however, Darling reports a fatal case of bacillary dysentery in which the Flexner type of organism was recovered in blood culture before death.

Multiple miliary abscesses of the liver occasionally are found at autopsy, but in the few cases reported the specific organism in this situation has occurred along with B. coli and other intestinal bacteria. With the exception of the degenerative changes in the internal organs extra-intestinal lesions are unknown in bacillary dysentery.

PROPHYLAXIS

Geographical.—Epidemics of bacillary dysentery have occurred from the earliest times throughout the tropics and temperate zones. At the present time epidemics are infrequent compared with the days before modern sanitation. However, small circumscribed epidemics break out occasionally in the congested districts of large cities. On the other hand, endemic dysentery is a common occurrence in asylums and public institutions. That form of the disease known as infantile diarrhea is prevalent in all large cities during the summer months. Indigenous dysentery is therefore of more importance nowadays than the epidemic form. In the tropics and temperate zones one form or another of bacillary dysentery is always to be found. Dysentery has always been one of the scourges of armies and army camps. By modern methods of sanitation it was kept out of the camps in the great World War. On account of the conditions necessarily existing at the front and in the trenches, dysentery was present there, though to a much less extent than in any previous conflict except the Russo-Japanese War. In general it may be said that wherever the hygienic conditions are bad, especially if the water supply is polluted with human excreta, dysentery is endemic and may become epidemic.

Epidemiology.—Outbreaks of dysentery in a locality have been attributed to other factors than the water supply; this is not because of any peculiarity of the soil or climate, but because new foci of infection are continually occurring. In recent years many of the most obscure facts concerning the dissemination of dysentery have been elucidated by the discovery of the intimate relation borne by dysentery patients and convalescents to the further spread of the disease. Dysentery bacilli always leave the body by way of the excreta, pass into the external world, and find their way into others indirectly through the alimentary tract.

Almost all large epidemics of dysentery are water-borne infections, mainly because of the too intimate connection between sewage disposal and water supply. There is the same epidemiological relation of the two in this disease as in typhoid fever, since the causal agent in both diseases leaves the body in the feces. Polluted well water is a common source of infection in country districts.

Dairy products and other foodstuffs which are consumed in the raw state may be important sources of infection, because infection invariably takes place by the ingestion of the bacteria in infected water or food contaminated by the feces of dysentery patients. Some epidemics of dysentery can be traced to infected milk which has been polluted by water used for the purpose of cleansing the cans or utensils employed for its transportation. Milk is undoubtedly an important factor in the spread of endemic dysentery, especially that in children.

Epidemics of more or less definite localization usually occur under conditions of crowded quarters in unsanitary environment.

The common house fly plays an important rôle as a mechanical carrier of the disease. This insect is especially concerned in the spread of endemic dysentery which is so prevalent among infants of congested city districts during the summer months. Undoubtedly flies have formerly played a rôle in spreading dysentery in army camps. Cases formerly attributed to dust may be reasonably ascribed to this insect. Furthermore, with infant dysentery the infecting agent may be transported directly from the infected to the healthy in the same or adjoining wards of a hospital through the medium of nurse or attendant. The slightest soiling of the hands with fecal material may be the means of spreading the disease. The stool from a case of dysentery should be as carefully disposed of as the dejecta from typhoid patients.

Bacilli Carriers.—We see no reason to doubt that the individuals who have recovered from acute dysentery may not harbor for months B. dysenteriæ in their intestinal tract. Since the Flexner organism may be a normal inhabitant of the gut (under ordinary circumstances an innocent one), and since it is conceivable that even the Shiga bacillus may persist in small numbers months after an acute attack, human beings, themselves apparently well, may serve as "carriers." Such "carriers" are, however, not entirely analogous to those of typhoid fever, for in the latter instance the gall-bladder becomes infected and serves as a lasting bacterial reservoir. They are, on the other hand, just as important as "typhoid carriers."

Agglutination Reaction.—The recognition of the type of infecting organism in every case of bacillary dysentery is of the utmost importance from the standpoint of treatment with an immune serum. Where such treatment is contemplated it is essential as a matter of routine to determine in every case by the agglutination reaction the type of the infecting organism.

Sera from patients suffering from bacillary dysentery, whether epidemic or endemic, agglutinate the specific organism. Therefore it may be said that the diagnostic value of the agglutination test in this disease is the same as the Widal reaction in typhoid. Bacteriolysins and other immune substances also appear in the blood of patients suffering with dysentery. The agglutinins are readily demonstrable on the third to the fifth day after the onset of symptoms. The blood from animals artificially immunized against the Shiga bacillus will agglutinate paradysentery bacilli, though not in as great a dilution as it will the Shiga organism. The converse is also true. Since the paradysentery organism may occur normally in the intestine, its mere presence in the feces of a dysenteric patient is no proof of its causal relationship to the disease. If, however, along with the demonstration of the organism in the bowel discharge, the serum from the patient causes clumping of the bacillus in dilutions 1 to 50 or higher, the infection may be pronounced dysentery due to that particular organism.

The isolation of the organism from the stool of a suspected case as a means of diagnosis is often disappointing even in the hands of the experienced laboratory worker. It requires at least forty-eight hours to determine the culture from the most favorable stool specimen, and often repeated examinations of a number of stools; so that the cultural method of diagnosis is of limited usefulness, except in conjunction with some one of the serum tests. However, in epidemics of dysentery which are due to the

Shiga organism the cultural method is of more importance than in endemic dysentery.

The precipitin and absorption tests for the differentiation of B. dysenteriæ are specific, but are not practical outside of the scientific laboratory.

The cutaneous reaction in the diagnosis of dysentery need only be mentioned, as it is of the least value of all of the serum tests. Though it will serve to diagnose dysentery from other intestinal diseases, it will not differentiate the type of organism, that is, whether the disease is due to the Shiga or some one of the paradysentery bacilli. The material used in this test is vaccine administered in the same way as tuberculin.

TREATMENT

Serum Treatment.—Shiga was the first to prepare and use successfully an immune serum for the treatment of acute epidemic dysentery. For endemic dysentery, or that form due to some one of the paradysentery group, he employed a polyvalent serum and claims to have reduced the mortality in Japan from 35 per cent to 9 per cent. That decided improvement follows its use in *epidemics* among adults there is no question. The conditions of success are that it must be used early in the disease before serious lesions have developed or a secondary infection has set in, which is a common occurrence in acute dysentery. The serum may be given intramuscularly or, in severe cases, intravenously. In the latter event it is necessary to determine by preliminary intradermal injections whether the patient is sensitized to horse serum, and, if he is, to desensitize him by small subcutaneous injections. In any event it is wisest to proceed by injecting a small amount, say 2 c.c., and waiting ten minutes before proceeding with the intravenous injection of the balance. Larger amounts than formerly are recommended for both intramuscular and intravenous use; 50 to 100 c.c. of the serum twice daily for two or three days, then once daily for two to three days.

It is important to determine the type of infection before giving the serum in order to know what serum to give. Though a polyvalent serum is advocated in all cases regardless of the type of infecting organism, it is far better to give only the serum specifically suited in the individual case. For example, the "Shiga" serum in the treatment of endemic dysentery due to the paradysentery bacillus (Flexner) is of no avail, and conversely. Acute dysentery is probably a true toxemia, its symptoms being referable almost entirely to the absorption of the specific toxin. Intravenous injection of the Shiga toxin will cause a violent diarrhea and intestinal lesions in the rabbit, but these results are not obtained with the injection of the toxic product from the paradysentery group of bacilli. The intestinal lesions are definitely shown experimentally to be due to the excretion of the toxin, and not due to the direct action of the bacilli upon the gut mucosa. This has been proved for the Shiga organism, but not for the paradysentery group, which might explain why in endemic dysentery the serum treatment is not so efficacious.

In endemic dysentery a polyvalent serum is indicated—that is, a serum in which the various paradysentery bacilli have been employed in the active immunization of the horse, since these organisms are subvarieties of the same species, and it is not practical to determine the particular subgroup responsible in a given case.

Vaccination.—Prophylactic vaccination for acute epidemic bacillary dysentery leads to practical results. Since it will protect the individual against subsequent infection for a period of eight to ten weeks its usefulness is apparent in preventing the spread of the disease in outbreaks of epidemics in asylums, institutions, camps, etc. Vaccination against dysentery has the same practical value in this disease as it has in typhoid. Active immunization in this manner should be insisted upon for nurse, attendant, and all persons associated or likely to come in contact with those suffering from the acute epidemic type of the disease.

The dysentery "vaccine" may be prepared after any of the standard methods. Virulent cultures of the specific organisms are first grown upon slanted nutrient agar for twenty-four hours, when the growth is washed down and thoroughly emulsified in sterile normal salt solution. The suspended culture is then killed by heating at 56° C. for thirty minutes, or it is carbolized in 1 per cent carbolic acid solution for twenty-four hours, after which it is standardized and tested for viability. The dose of the killed culture (vaccine) is given hypodermatically and varies from 500,000 to 1,000,000 bacilli or more. In administering the "vaccine" as a prophylactic it is well to repeat the injection in two or three days, using double the amount of the initial dose. A local subcutaneous reaction at the site of inoculation usually follows in twenty-four to thirty-six hours and may be looked upon as a favorable sign. In some instances the injection occasions constitutional symptoms with one to two degrees of fever. It may be stated that the more marked the reaction, both local and constitutional, the more effective and lasting is the acquired immunity. While vaccine therapy is recommended as a preventive in acute epidemic dysentery (Shiga) under the conditions above mentioned, its promiscuous use is not advocated, since it is impracticable. This has reference to its use as a preventive against the spread of endemic or sporadic dysentery.

Statistics show that vaccination as a curative agent for dysentery has not given brilliant results. This might be due in part to the use of a "stock" vaccine where a "personal" or autogenous culture should have been employed. Where the specific organism can be isolated the vaccine should be prepared from it and not from stock culture if the best results are to be obtained.

Theoretically, in the so-called chronic form of endemic bacillary dysentery, where the specific organism (paradysentery bacilli) still lurks in the deeper layers of the gut, the use of a polyvalent vaccine (prepared from the various strains of paradysentery bacilli) is indicated. However, in the large percentage of these cases, the initial excitant has disappeared and the intestinal condition is prolonged by some one or more of the normal inhabitants of the intestine, such as the streptococcus, pneumococcus, and staphylococcus. Therefore, it seems more reasonable to employ a "vaccine" specific for these organisms and not one calculated only to be of use against the primary causal factor.

Treatment Other Than Specific.—What is here written applies to all forms of bacillary dysentery of whatever group. The symptomatology and general course of the disease are the same whether the infecting organism be of the Shiga or the paradysentery type (Flexner). Hence the treatment of the epidemic (Shiga) dysentery is the same as that of the endemic (sporadic) and institutional dysenteries. At the outset, it is to be remembered that we have to deal practically with two consecutive conditions, namely, the acute infectious disease which is more or less self-limited and the sequelæ of this acute infection. For we must regard the long-protracted diarrheal conditions not as a continuance of the disease itself, but as a true sequela, separate and distinct anatomically and bacteriologically from the initial disease.

Treatment of Acute Stage.—A patient with acute bacillary dysentery should be treated in many ways like one with typhoid fever. As in the latter disease, so in bacillary dysentery, nursing is of prime importance, not only to the patient himself but to his immediate environment and to the community at large (see under Prophylaxis). Absolute rest in bed is essential in all cases, for physical exertion otherwise incidental to the numerous bowel evacuations adds to the prostration caused by the toxemia and the pain. It is strange to see dysentery patients (even severe cases) permitted to alternate constantly between bed and commode, and that, too, by physicians who would be scandalized by the thought of permitting this in mild typhoid cases. The arrangement of the bed is of considerable importance. It should, if possible, be of the usual hospital type, a single narrow bed, fairly high, as this will permit the easy handling of the patient and the convenient adjustment and removal of the bed-pan without unnecessary exertion on the part of the patient or nurse. In this way, too, will be avoided any accidental spilling of bed-pan contents and contamination of bed and personal linen probable under more awkward and inconvenient arrangements. The mattress should be protected by a rubber sheet, and over this should be placed sheet and draw sheet. In many cases desire to go to stool is so frequent as to be practically constant, and in these cases the patients insist on having the bed-pan under them for long periods at a time, so that the construction and form of the bed-pan are more than ever of importance in that it should be as comfortable and cause as little trouble as possible by pressure. (It must be conceded in this connection that there are patients who insist on using the commode on account of the annoyance of the bed-pan, and will not consent to remain in bed until forced to do so by their own prostration and weakness.) Scrupulous cleanliness of the patient must be insisted upon, care being taken upon this point, not only after each use of the bed-pan, but also by the usual daily general cleansing bath. Aside from this, it is not usually necessary to use baths except in cases with fever. In such cases cool, gentle sponging or toweling of the trunk and limbs and the ice-cap applied to the head are the most satisfactory forms of hydrotherapy.

Hot-water bags or large poultices to the abdomen add greatly to the patient's comfort.

Feeding.—Here the limitations are narrow, and the problem presented by the indications and contra-indications is a puzzling one. Physiological rest for the damaged organ would seem to be our first consideration. In the beginning the wisest course is total abstinence from food leaving a residue. In this category milk must, of course, be included. Milk however administered, whether raw or boiled, must be considered only a quasiliquid food. In the stomach the casein is immediately precipitated, and the food is henceforth a solid, and likely to set up peristalsis upon entering the intestine. An additional objection to milk is that it furnishes a fine culture medium for the intestinal flora. The pediatrists have long since seen the wisdom of immediately withdrawing milk upon the slightest bowel disturbance. It is a lesson we should learn to apply in the treatment of adults. On the other hand, in the face of the toxemia and the excessive loss of fluids, we must not, in our zeal to protect the intestine from injurious influences, carry on the starvation too far or too long, nor fail to supply fluids in quantities sufficient to countervail the excessive outgo. The patient should be urged to drink freely, but the fluid *must not be cold.* While we cannot supply anything like sufficient caloric values, still, by the use of strong broths, albumin water, whey, barley water, as well as of alcohol in conjunction with extractives (in the form of the various proprietary so-called foods) we can furnish a valuable amount of stimulation as well as a small amount of the calories needed. In this connection it would seem that the suggestion of Kendall with regard to the use of lactose in infantile diarrheas would be of considerable value. There is no reason why we should not, by adding lactose to the various drinks, contribute largely to the sum total of calories furnished. In addition to this, if Kendall's reasoning is correct, we may, through the lactose, favorably affect the intestinal bacteria in the sense of giving the normal flora of gas-producing bacilli the upper hand over the Bacillus dysenteriæ and thereby directly influence the further course of the disease. The administration of water is of greatest importance in the acute stage. Patients may be persuaded to take and prefer water in the form of decoctions and infusions so as to do away with the flat taste. The tisanes of the French, such as orange leaf tea, bay leaf tea, geranium tea, are exceedingly grateful and pleasant. After some days of this meager diet, and when symptoms begin to ameliorate, it will be permissible to add milk, at first diluted and, perhaps, even predigested when necessary. Some authors claim that boiled or pasteurized milk is better cared for than raw milk. Not until the patient has entirely recovered and has been without symptoms for a week at least should we venture to increase his dietary by the inclusion of soft foods (cereals, soft-boiled eggs, etc.). From then the return to the normal diet should be slow and gradual, meat, puréed vegetables (potatoes, carrots, etc.), and puréed fruits being successively added. Not for weeks should the patient be allowed to eat raw fruits or bulky vegetable food.

Drugs.—All unite that it is impossible to check the diarrhea at once by astringents and opiates, and unwise to attempt to do so. All equally unite in recommending a preliminary and thoroughgoing cleaning of the bowel by purgation. For this purpose some prefer castor oil, not only on account of its efficiency, but also because of the subsequent constipating effect attributed to it. It may be given in an initial dose of ℥ss to ℥i (15 to 30 c.c.), or in small repeated doses.

Calomel may be given in one dose of 5 gr. (0.3 gm.), or in broken doses of ⅙ gr. to ¼ gr. (0.01 gm. to 0.015 gm.) every half hour until stools become fecal. Magnesium (or sodium) sulphate has supporters equally as ardent as those of castor oil and calomel. There is no doubt as to its great value in the large majority of cases. It seems best to give at the outset one large dose, ℥ss to ℥i (15 to 30 gm.), and to follow with smaller doses (ʒii, 4 gm. every two to four hours. A formula, which has done excellent service, is:

℞	Magnesii sulphat.	(30.0)	℥i
	Tr. opii deodorat.	(8.0)	ʒii
	Ac. sulphuric aromatic.	(8.0)	ʒii
	Aq. menth. pip. ad.	(180.0)	℥vi

Sig.—Tablespoon every three hours.

Here the opium is given for the relief of pain. The sulphuric acid is said to be of value because of its astringent action. The prescription should be given until the stools cease to be bloody and become fecal in character.

It has also been suggested that sodium sulphate solution (2 to 4 per cent) may be used by the transduodenal lavage method as a satisfactory method of flushing the colon.

In addition to these remedies by the mouth it may become necessary to use morphin by hypodermic injection for the relief of pain. The tenesmus is best treated by the rectal injection of 1 to 3 ounces (30 to 90 c.c.) of starch water to which has been added 15 to 20 drops (1 c.c.) of laudanum. When this does not succeed we may have recourse to suppositories of

℞	Pulv. opii	gr. 1	0.065 gm.
	Ext. belladonna	gr. ¼	0.015 gm.

Daily irrigations of the bowel with large quantities of salt solution are most valuable. Injections and irrigations of the bowel with other solutions are not of much avail in this acute stage, but are better adapted to the chronic stage.

In the acute stage it is often necessary to supply the body with fluids to replace the large quantities lost in the stools. For this purpose normal saline is given by hyperdermoclysis or intravenously.

Treatment of Chronic Stage.—Two main facts are to be borne in mind. First, the bacteria which are responsible for the disease are no longer present in numbers and do not play a rôle in the continuance of the symptoms. We have chiefly to deal with the secondary invaders, in the main streptococci. Second, this stage is truly a surgical condition, and to be treated as such. The bowel wall, especially at the flexures, is the site of numerous ulcers. Many of the latter are located in the rectum and sigmoid, within reach of the endoscopic instrument, through which they can be treated by direct topical applications of nitrate of silver (pure stick or in strong solution). Or we may try to reach these as well as those higher up by irrigations. It is customary to use silver nitrate in solution of 1:500 to 1:1,000, or even weaker strengths. Irrigations should be used with large quantities of fluid—at least 1 or 2 quarts—and the bowel should be subsequently flushed with salt solution to neutralize the excess of silver solution remaining in the gut. Other injections recommended are tannic acid, ¼ to ½ per cent; thymol, 1:500 to 1:1,000; methylene-blue, 1:5,000; corrosive sublimate, 1:10,000; resorcin, 1 to 2 per cent; creolin, 1 to 2 per cent; lysol, 1 per cent.

When the disease persists through months and we are face to face with a state of affairs which threatens the life of the patient through inanition we are forced to consider more radical measures. Appendicostomy and irrigation of the colon and rectum from above have been recommended, but no brilliant results have been reported. In extreme cases it might be possible by a right-sided colostomy and the creation of an artificial anus to give complete physiological rest to the colon and the rectum just as is done in malignant diseases of the lower bowel (with which, indeed, the condition has many features in common). After the ulcers have been healed and the patient has been restored to health a secondary operation would be performed to do away with the artificial anus and restore the normal state of affairs.[1]

The use of drugs by the mouth has not been reported as satisfactory by most writers. Bismuth has been recommended with the idea of coating the ulcers, but it not only fails to do this but is open to the further objection that it frequently causes a false obstipation, and when the mass of accumulated bismuth has been removed from the rectum the diarrhea begins afresh. Intestinal antiseptics, such as benzonaphthol, salol, and the like, have been given, but without brilliant results. Equally futile are astringents, such as lead salts, tannin, and its derivatives.

Diet in Chronic Cases.—Much greater freedom can, of course, be permitted in the chronic stage than in the acute stage. Milk, eggs, cereals, meat in small quantities, and even purèed vegetables may be permitted. The diet must, of course, be individualized. In no case should food having large, coarse residues be allowed.

BACILLARY DYSENTERY IN CHILDREN

WILBURT C. DAVISON

Bacillary dysentery in children was established as a bacteriological and clinical entity in 1902, and was then clearly differentiated from that indefinite group of diarrheal conditions known for the past two centuries as cholera infantum, ileocolitis, infectious diarrhea and summer complaint.

The *onset* is usually sudden. The child loses his appetite and becomes restless and irritable. His temperature rises and he may vomit. Many patients have convulsions. Within a few hours the stools become more frequent. These are at first fecal but soon are composed of quantities of mucus. Blood usually appears in the stools on the second or third day. Tenesmus and straining are common symptoms. The number of the stools may be as high as thirty per day and may consist of merely a tablespoonful of blood, pus and mucus. Nausea and loss of appetite are probably more common in dysentery than in any other condition, so the *course* of the disease is marked by dehydration and emaciation, due to the reduction in the amount of food ingested as well as to the great loss of fluid from the bowel. In mild or moderately severe infections, the fever lasts from but a few hours to six or seven days, the blood disappears from the stools at the end of the first week and the diarrhea ceases by the fourteenth day. In severe infections, most of which are fatal, the temperature may remain at 102° to 104° F. and the stools continue to be frequent, bloody and purulent. Two-thirds of the deaths occur within the first twelve days of the disease.

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[1] The editor has had under observation for some years a patient in whom this procedure was successfully carried out.—Editor.

Physical examinations reveal little except emaciation and dehydration. The spleen is rarely palpable. Very rarely the thickened colon may be felt. The average white blood-cell count is 12,000 per c.mm. The mortality is very much lower in patients with a leukopenia, that is, white blood-cells less than 8,000 per c.mm., than in those whose white blood-cells are above 20,000 per c.mm. A high white blood-cell count is usually regarded as an index of the patient's dehydration rather than a true leukocytic response to the dysenteric infection.

Complications are uncommon. Otitis media, ulcerative stomatitis, pyelitis and bronchopneumonia are sometimes encountered, but no more frequently than in other diseases of the same severity. Acidosis of the acetone-body type may occasionally occur.

Relapses are rare, although there may be a reappearance of blood in the stools if the patient suffers from some febrile complication. Reinfections are extremely unusual.

Clinical Diagnosis.—The differential clinical diagnosis is usually not difficult. It has been proved that 90 per cent of all patients who suddenly develop diarrhea accompanied by fever, vomiting and bloody stools, are suffering from bacillary dysentery. A prolapse of the rectum, intussusception, rectal polypi and excoriated buttocks must, of course, be eliminated as causes of blood in the stools. As a matter of fact a prolapse of the rectum is not an infrequent result of the straining that accompanies bacillary dysentery. Amebic dysentery is so extremely rare in children in this country that it may almost be disregarded as a cause of bloody diarrhea. The clinical diagnosis of bacillary dysentery in a patient who does not pass blood in the stools is extremely difficult and in fact almost impossible without bacteriological assistance. This mild type of infection, although frequent in adults, is unusual in children.

Bacteriological Diagnosis.—A definite bacteriological diagnosis, either by stool cultures or by agglutination tests, can be made in practically all instances. During the period in which the patient is passing blood or pus, stool cultures are positive in 50 to 60 per cent of the cases. If stool cultures are repeated, this percentage may be even higher for, with rare exceptions, the number of dysentery bacilli in any stool culture is very small and they easily may be overlooked. Dysentery bacilli are much more frequently found in the dysenteric stools of children than in those of adults. This difference is probably due to the fact that children pass a larger amount of pus and blood and a smaller amount of fecal matter, so that the proportion of the dysentery organisms to the saprophytic intestinal bacteria is greater. The simplest procedure for the isolation and identification of dysentery bacilli consists in culturing a portion of the stool on plates of Teague's medium and then determining the agglutination and biological reactions of any non-fermenting colonies that may occur. Should stool cultures fail to determine the diagnosis, the agglutination reactions of the patient's serum should be tested after the first week of the disease in much the same way as with the Widal reaction in typhoid fever. Agglutinins for the infecting dysentery bacilli appear in the patient's serum from the sixth to the tenth day after the onset and remain for at least six months. The agglutination reaction in dysentery is of the greatest assistance provided that a standard method is used and that the patient's serum is tested against the six most common types of dysentery bacilli. Dysentery bacilli are divided into two main groups, Shiga and Flexner. The former ferment dextrose but not lactose or mannite, are non-motile, and do not produce indol. They produce an endotoxin which gives rise to intestinal symptoms and an exotoxin which causes nervous manifestations. The bacilli of the Flexner group ferment dextrose and mannite but not lactose, are non-motile, and usually produce indol. They produce only an endotoxin. Flexner bacilli have been subdivided into several subgroups by two different methods: (1) biologically, by means of their fermentation reaction in maltose and saccharose media; and (2) serologically, by means of agglutination tests with sera made from single strains. Inasmuch as these biological and serological subdivisions do not coincide and as the former are changeable, it is usually preferable to adhere to the English serological classification and to refer to these subgroups as Flexner, V, W, X, Y and Z. In addition to the Shiga and Flexner bacilli, there are probably other varieties which may occasionally be encountered. In this country, in children, Flexner dysentery occurs about ten times more frequently than Shiga infections. Mixed infections are extremely uncommon. Dysentery bacilli are rarely if ever found in the stools of normal infants or of those who are suffering from simple diarrhea. B. welchii (gas bacillus), B. morgan, B. pyocyaneus, B. proteus, Streptococcus fæcalis and virulent B. coli are of no etiological importance in dysentery or in simple diarrhea.

Clinically, in children, it is impossible to distinguish between infections with one or the other of these groups of dysentery bacilli. The clinical picture and severity are almost identical, although it is stated, but not proved, that the mortality in Shiga dysentery is much higher than in the Flexner variety. In adults, on the other hand, Shiga infections may sometimes be distinguished by their greater severity.

Pathogenesis.—The pathogenesis of dysentery is apparently explained by the ingestion of the bacilli with food, and the subsequent inflammation of the intestinal mucosa. The latter is probably a result of the direct action of the endotoxins that are liberated by the breaking down and autolysis of the bacterial cells. There is no evidence that dysentery is primarily a septicemia as is typhoid fever. Positive blood cultures are extremely rare. The intestinal lesions are identical in Shiga and Flexner infections. In Shiga infections in adults, lesions of the central nervous system similar to those of poliomyelitis and encephalitis have been described. These are due to the Shiga exotoxin. However, in children, death or recovery usually occurs before the central nervous system is affected.

Pathology.—The pathological lesions of this disease, in strong, well-nourished children who die as a direct result of the dysenteric infection, even in those who die within three days of the onset, usually consist of a pseudomembrane which may be limited to part of the colon or may extend from the ileocecal valve to the anus. Occasionally, the last few inches of the ileum may also be affected. In the majority of instances, portions of this pseudomembrane become separated from the intestinal wall, leaving ulcers with clean surfaces, elevated, non-undermined edges and a base formed by the submucosa. Occasionally, fatty degeneration of the liver may be found. In patients who have succumbed indirectly to dysentery, that is, those in whom some concomitant condition, such as scurvy, rickets or pneumonia, has been the direct cause of death, the intestines may be merely hyperemic or a slight ulceration of the lymph follicles of the lower third of the ileum and colon may be present. A terminal dysenteric infection in weak, poorly nourished infants may cause deep ulceration of the colon.

Treatment.—The expectation that efficacious *specific therapy* would follow the discovery of the etiological factor in this disease has so far been vain as far as children are concerned. In adults serotherapy has been successful, especially in Shiga infections, but subcutaneous and intramuscular injections of antidysenteric serum have not reduced the mortality in children except possibly in a few patients who were treated within the first three days of the disease. Vaccine therapy has not been beneficial nor have injections of peptone and other foreign proteins. The work of Twort and d'Herelle on bacteriophages or bacteriolysants aroused new hope for specific treatment. It was found by these and other investigators that filtrates of stool cultures would kill and dissolve dysentery bacilli in vitro. Unfortunately these filtrates produce no effect when fed to or injected into infants suffering from dysentery. A further opportunity for specific therapy may lie in Besredka's theory of localized intestinal immunity. He believes that the intestinal wall is the barrier at which the dysentery bacilli must be attacked. If this view is correct, antidysenteric serum to be effective must be introduced directly into the lumen of the bowel. This method of administration may be possible by means of a duodenal tube but as yet it has not been attempted.

At present the treatment of bacillary dysentery is entirely symptomatic. Dysentery produces most of its damage in three ways: (1) by the loss of body fluid and dehydration; (2) by the inflammation of the intestinal mucosa and the absorption of toxic products; and (3) by the nausea and loss of appetite. The replacement of the fluid loss is perhaps the most important therapeutic feature. Water, sweetened if necessary with ½ gr. saccharin to every 8 ounces, should be offered to the child every hour in unlimited quantities.

Intraperitoneal Injections.—If the dehydration is marked, as shown by the loose skin, dry lips and tongue and sunken eyes, 100 to 400 c.c. sterile normal (0.85 per cent) salt solution, depending upon the size of the patient, should be injected intraperitoneally. It may be necessary to repeat this procedure several times at intervals of twelve to twenty-four hours if the patient continues to lose quantities of fluid in his stools and refuses to take sufficient water by mouth.

Technic of Intraperitoneal Injection of Saline.—A graduated liter gravity flask, fitted at the lower end with 3 feet of rubber tubing (¼ inch internal diameter), to the distal end of which a tapered glass nozzle is attached, is completely wrapped in at least two thicknesses of muslin and sterilized in an autoclave at 15 pounds pressure for 30 minutes. A short beveled needle of 17 to 19 gage, 2 inches in length, fitted at the hilt with 3 inches of rubber tubing (3/16 inch inside diameter), is sterilized by boiling for 10 minutes. A sterile 300 to 500 c.c. flask of 0.85 per cent sodium chlorid (in distilled water) is placed in warm water (100° F.) for 10 minutes. After the patient has voided or after the bladder has been emptied by gentle pressure over it, a circular area, 4 inches in diameter, on the patient's abdomen between the pubis and the umbilicus is cleansed by the successive application of iodin and alcohol. The passage of a rectal tube will often relieve any abdominal distention that may be present. The sterile gravity apparatus is then unwrapped and suspended 2 feet above the patient's head. The sterile needle is attached by its rubber tubing to the glass nozzle and the warm sterile saline is poured into the gravity flask and the air expelled from the tubing. The needle is then inserted through the cleansed area of the abdominal wall into the peritoneal cavity and the saline allowed to flow in slowly until the abdomen fills. Injections of 100 to 400 c.c. may be made, according to the size of the child, but the amount should not be so great as to produce overdistention of the abdomen or respiratory distress.

Saline, 0.85 per cent, is probably the best fluid for intraperitoneal injection, as 5 per cent glucose and 4 per cent sodium bicarbonate may give rise to a sterile, fibrinous exudate. A hypodermic syringe containing ½ gr. caffein, or 10 minims epinephrin hydrochlorid, should be prepared for use in case of collapse.

Nasal Drip Method.—Though intraperitoneal injections are readily performed in hospitals, they are sometimes difficult under home conditions, or if there is distention of the patient's abdomen which cannot be relieved by the passage of a rectal tube. In such cases, fluid, either normal saline, 5 per cent glucose, or boiled tap water, is easily administered directly into the stomach by the nasal drip method, by means of a continuous drip apparatus attached to a nasal tube which is fastened in place with adhesive plaster.

A nasal drip delivering fifteen drops per minute may be continued four or five days without producing nausea. Occasionally, however, the nasal tube may cause serious erosions of the esophageal membrane. The nasal tube should be *removed* and *cleaned* once or twice daily. The nasal drip may be continued without intermission or preferably in periods of a half hour alternating with equal periods of rest. By this method, 500 to 1,000 c.c. of fluid may be given daily. If the infant has persistently refused his feedings, protein milk or buttermilk may also be administered through the nasal tube by disconnecting the drip apparatus and connecting a funnel.

Technic of Administration by Nasal Drip Method.—A catheter (10 gage French) is inserted into the esophagus through the nostril and the upper end securely fastened to the face with adhesive plaster. It is usually necessary to restrain the child by pinning his sleeves to the sheets. A graduated liter gravity flask, fitted at the lower end with 1 foot of rubber tubing (¼ inch internal diameter) and a screw pinch cock, is suspended 2 feet above the patient's head. To the distal end of this rubber tubing is attached a drip apparatus, that is, a glass tube, 6 inches in length and 1 inch in internal diameter, tapered at the lower end to fit ¼ inch rubber tubing and tightly fitted at the upper end with a rubber cork in which are two holes. In one of these holes is inserted a piece of glass tubing 3 inches long and ¼ inch internal diameter. The rubber tubing from the gravity flask is attached to this glass tube. The other hole acts as an air vent. The tapered lower end of this drip apparatus is fitted with 2 feet of rubber tubing (¼ inch internal diameter) to the distal end of which a tapered glass nozzle is attached. This glass nozzle is inserted into the upper end of the nasal catheter. The flask is filled with fluid, either 0.85 per cent saline, 5 per cent glucose, or boiled tap water, and the flow regulated by the screw pinch cock.

Subcutaneous Injections.—Subcutaneous injections of saline are sometimes painful and do not usually allow the administration of sufficient fluid. They may be given, however, if a nasal drip apparatus is unobtainable, to children in whom abdominal distention cannot be relieved by the passage of a rectal tube. Fluid administered by rectum, either by syringe or a continuous drip apparatus, is seldom retained or absorbed by children.

Intravenous Injections.—If the dehydration is of an extreme degree or if symptoms of acidosis are present, that is, drowsiness, and deep, slow respirations (hyperpnea), sterile 5 per cent glucose should be injected *intravenously* in amounts of 10 c.c. for each pound of the patient's weight. This procedure may be repeated if necessary after from twelve to twenty-four hours. Occasionally the intravenous injection of 5 per cent glucose will not correct the acidosis and the administration of sodium bicarbonate may be necessary. The latter should be given *intravenously* as a 4 per cent solution in amounts of 10 c.c. per pound of body weight. Sodium bicarbonate by mouth will seldom prevent or cure acidosis and, furthermore, may produce nausea and abdominal distention.

Technic of Intravenous Injection of 5 Per Cent Dextrose.—A graduated 100 c.c. gravity flask, fitted at the lower end with 18 inches of rubber tubing 3/16 inch (internal diameter) to the distal end of which is attached a metal connection adapted to Luer syringe needles; a 10 c.c. Luer syringe and two short beveled needles of 20 gage, 1¼ inches in length, are sterilized by boiling for 10 minutes. A sterile 300 to 500 c.c. flask of 5 per cent glucose is placed in warm water (100° F.) for 10 minutes. The skin over the patient's vein should be cleansed as previously described (intraperitoneal injection). The veins in order of choice for intravenous injections are the arm veins, the external jugular veins, the femoral veins, the foot and scalp veins and, *only as a last resort,* the longitudinal sinus (provided, of course, that the patient's anterior fontanel is open). The warm sterile glucose is poured into the gravity flask, the air expelled from the tubing, and the tubing clamped with the thumb and first finger to prevent the escape of the fluid. A sterile needle is fitted to the syringe and the vein punctured. As soon as blood is aspirated into the syringe (indicating that the needle is in the vein) the syringe is disconnected from the needle and the gravity apparatus connection quickly inserted into the needle. The 5 per cent glucose should flow in slowly (5 c.c. per minute).

Preparation of 4 Per Cent Sodium Bicarbonate for Intravenous Use.—Five hundred c.c. of distilled water should be sterilized in an autoclave at 15 pounds pressure for 20 minutes or, in cases of emergency, by being boiled for 30 minutes. When the water is completely cooled, 20 gm. pure sodium bicarbonate, if possible from a freshly opened bottle and weighed in a sterile container, should be added. The resulting 4 per cent sodium bicarbonate solution, as far as can be determined, is always sterile. It should be warmed to body temperature and injected intravenously as described in the preceding paragraph.

Intravenous injections of citrated blood from a donor of the same blood group in amounts of 10 c.c. per pound of body weight have been beneficial, especially in those patients who have failed to progress after the acute febrile stage of the disease has passed. Only those fitted by special training should perform blood transfusions. If the blood from the donor has been found to be compatible with that of the patient (blood grouping), it is aspirated into sufficient sterile 10 per cent sodium citrate to make a final dilution of 0.25 to 0.5 per cent of the latter. It is then injected intravenously by the same technic as that outlined for the intravenous injection of 5 per cent glucose. Serious reactions in children as a result of transfusions with citrated blood are very uncommon.

Quiet and Rest Essential.—Rest in bed is of course essential. It is frequently necessary to prescribe paregoric in doses of 5 to 10 minutes after every stool in order to relieve the straining and tenesmus and to insure a certain amount of sleep. The maximum amount of paregoric given daily should of course depend upon the age and size of the patient. Aside from paregoric and morphin, drugs are of but little assistance in dysentery. Bismuth subcarbonate, kaolin and animal charcoal, though harmless, usually do not relieve the intestinal symptoms. Castor oil, calomel and other purgatives should not be given, except possibly during the first day of the disease. *Enemata* and *colonic irrigations* of small amounts of warm starch solution, normal saline or 4 per cent sodium bicarbonate often relieve the tenesmus by cleaning out the rectum and lower colon. Inasmuch as dysentery so seldom becomes chronic in children, colonic irrigations of tannic acid, and other astringents which are recommended in protracted cases in adults, are not often necessary.

Diet.—There is great diversity of opinion in regard to the nature and quantity of the *diet* for children suffering from dysentery. If the patient is nauseated, nothing but water should be given for the first 12 to 24 hours. When the vomiting has ceased the patient should be fed with 1 or 2 ounces of *protein milk* at 4-hour intervals. This amount should then be gradually increased up to 7 ounces at each feeding in accordance with the caloric requirements of the infant. As a general rule, if the patient is less than 6 months of age, he should receive 6 feedings per day; if between 6 and 12 months, 5 feedings; and if between 1 and 2 years, 4 feedings. When the stools have become fewer in number and "semiformed," ½ ounce of some mixture of dextrin and maltose may be added to every 20 ounces of protein milk. This may be increased to 1 ounce if the stools continue to be formed. Four to 6 days later, if the diarrhea has not recurred, 1 feeding of cow's milk mixture suitable to the patient's age may be substituted for 1 feeding of protein milk. This substitution may be repeated every other succeeding day until all of the infant's feedings consist of cow's milk. Cereals and other articles of food may then be added gradually until the patient receives a diet that is normal for his age and weight. This complete change in diet may require several weeks. Should the transition from a diet of protein milk to one of a cow's milk mixture result in more numerous stools, it is advisable to return to the protein milk for several days or even weeks longer and then cautiously to reattempt the transition. Orange juice and cod-liver oil must be omitted from the diet during the acute stage of dysentery.

Directions for Preparation of Protein (Eiweiss) Milk.—Heat 1 quart of whole milk (not repasteurized) to 98° to 100° F. for 5 minutes. Add 4 teaspoonsful of liquid rennet, stir and leave at room temperature for 1 hour. Cut the resulting curd into 2-inch squares and place them in a piece of cheesecloth and hang in a refrigerator 2½ hours, or longer, if necessary, until the curd is well drained and dry. The caloric value of this curd or junket is 45 calories per ounce.

Force the curd from 1 quart of milk (prepared as in the preceding paragraph) through a potato ricer, then through a sieve covered with one thickness of cheesecloth, by means of a plain wooden potato masher or wooden spoon. When the curd is thoroughly broken up, suspend it in 1 pint of cold sterile water. When the curd and water have been thoroughly mixed, add 1 pint of skimmed lactic acid milk. The curd from 1 quart of whole milk plus 1 pint of water and 1 pint of skimmed lactic acid makes approximately 38 ounces of protein milk. The caloric value of protein milk is 13 calories per ounce.

A more concentrated though somewhat less constipating form of protein milk may be prepared by emulsifying the curd from 1 quart of milk directly in a quart of skimmed lactic acid milk (omitting the pint of water). The caloric value of this concentrated protein milk is 22 calories per ounce.

Be careful, when warming protein milk to feed a patient, not to heat above 100° F. as the curd will toughen rapidly. Shake the protein milk well before feeding the patient.

If the patient is younger than 4 months or is in critical condition, it is sometimes preferable to give him 1 to 4 ounces of woman's milk and 1 to 4 ounces of skimmed lactic acid milk at alternate feedings, instead of a protein milk diet.

To an infant over 5 months of age whose appetite is good, 1 to 2 ounces of curd (junket) without whey may be fed by spoon at 1 or 2 feedings daily after the feeding of protein milk.

In those instances in which a breast-fed infant suffers from dysentery, the breast feedings at 4-hour intervals should be continued. If the number of stools is excessive, 1 to 4 ounces of skimmed lactic acid milk should be given to the patient immediately before each nursing.

Infants who persistently refuse food and premature infants may be fed by gavage (stomach tube) or by medicine dropper. If the infants refuse water, 1 to 4 ounces of water may be added to the gavage feedings. It was formerly customary to wait until the second week of the disease before commencing to gavage dysenteric patients who persistently refused food. It is possible, however, that undue delay in administering food forcibly may result in such a degree of malnutrition that the patient may fall an easy victim to his dysenteric infection. It is probably a better practice to administer, even during the first few days, a high protein, buttermilk diet in amounts of 75 to 100 calories per kilogram of body weight, using a stomach tube if necessary. If a patient vomits the greater part of his feedings, he should be fed by gavage. An infant is less likely to vomit his gavage feedings if the stomach tube is introduced through the nose. For patients who must be tube fed for several days, because of nausea or of total lack of appetite, it is often preferable to concentrate the protein milk by omitting the pint of water usually used in its preparation (concentrated protein milk) or to add 2 to 3 per cent of some mixture of dextrin and maltose even though the stools are still numerous.

Dysentery in children over 2 years of age is usually mild and a whole milk diet is often prescribed for the first four or five days. Eggs, cereals, broth, meat and finally green vegetables are then gradually added. However, in severe infections in children over 2 years of age, the diet should be similar to that outlined above for infants.

The *prognosis of* dysentery in children is much more grave than in adults. The latter rarely succumb to Flexner infections and the adult mortality in Shiga dysentery, in this country at least, is not high. In children under 3 years of age, however, the *mortality* even in Flexner infections is over 30 per cent. Under the age of 12 months the mortality is 45 per cent. If patients, who have mild infections and who pass a few blood-tinged stools for one or two days, are excluded, the mortality is 58 per cent. The presence of malnutrition, previous intestinal disturbances, pneumonia and rickets increases the gravity of the prognosis. The average age of the children who suffer from dysentery is 10 months, which would seem to indicate that infants are very susceptible to this disease, for all ages are more or less equally exposed to infection.

Bacillary dysentery is apparently spread by flies, contaminated fingers and mild unrecognized adult cases. Inasmuch as Flexner dysentery in adults may give rise to but a slight diarrhea for only twenty-four hours, it is possible that many infants are infected from such cases. Although adult dysentery carriers are not infrequent, they are extremely uncommon among children. Dysentery is very rarely disseminated from a central water supply or a dairy. Milk, however, is frequently infected in the individual homes by flies and careless handling. Dysentery is comparatively rare among breast-fed infants and among those who receive milk that has been boiled directly in the nursing bottles.

Prophylaxis.—Inasmuch as the treatment of dysentery in infants has not materially reduced the mortality, its *prevention* is most important. Inoculations with sensitized dysentery vaccines have been successfully used in the prevention of dysentery among troops, but they have not as yet been attempted in children. Infants and their food must always be protected from individuals who have diarrhea, regardless of its character, as well as from flies. The disease both in adults and children should be reported to the health authorities and quarantine instituted until three negative stool cultures at 24-hour intervals are obtained. If a normal child cannot be breast fed, his milk or milk mixture for the whole day should be divided into the requisite number of feedings. Each feeding should be poured into a clean nursing bottle. This should be plugged with non-absorbent cotton. All of the bottles should then be placed in a pan of cold water which should be heated to the boiling point and held there ten minutes. These boiled bottles of milk should then be kept on ice until needed. An infant over 3 months of age receiving boiled milk requires a tablespoonful of orange juice and a teaspoonful of cod-liver oil daily to prevent scurvy and rickets.

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CHAPTER XVI

BACTERIAL FOOD INFECTIONS

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Introduction.—It is probable that more disease is contracted through the consumption of food and drink than through any other medium, and the diseases which may be thus acquired are numerous and varied.

To summarize briefly:

Excessive consumption of wholesome food may lead to immediate distress and to ultimate obesity or other chronic metabolic disturbances, whereas the effect of insufficient food is manifested by the various phases of malnutrition.

Improperly balanced diet, consisting of good food in which the vitamins are lacking, or in which they have been destroyed by improper preparation, may lead to the onset of the so-called insufficiency diseases, scurvy, pellagra, beriberi, etc.

Foods which are wholesome to the majority of people may cause distressing allergenic symptoms, urticaria, asthma, etc., because of some peculiar idiosyncrasy or sensitization of certain individuals.

Foods which are originally wholesome may become harmful because of the addition of various chemical substances, either deliberately for their preservative action or accidentally during the process of manufacture and preparation.

Poisonous fish, occurring especially in the tropics, or poisonous plants, such as certain members of the mushroom family, may be mistaken for edible forms and cause serious illness or death.

The tissues of animals which harbor certain animal parasites such as trichina or tænia may be the medium through which human infection with these parasites is acquired. This is especially liable to be the case if the meat is not thoroughly cooked before it is eaten.

The tissues and milk from animals which are suffering from certain bacterial infections may be the medium of transmission of these infections to man.

Food which is originally wholesome may become contaminated with pathogenic bacteria through being handled by persons who are suffering from certain bacterial infections or who are bacterial carriers, and so transmit the disease.

Preserved foods which have been imperfectly sterilized and which happen to have contained spores of the Bacillus botulinus may become contaminated with the botulinus toxin and be the cause of botulinus intoxication.

It at once becomes apparent that the majority of the illnesses just enumerated have nothing whatever in common, except that they may be produced or transmitted by materials which are consumed as foods, and there is no term which can be properly applied which includes them all. The use of the term *ptomaine poisoning* to describe these cases should be discontinued for reasons which have been discussed in another chapter.

The term *food poisoning* has been defined by Jordan as including the occasional cases of poisoning from organic poisons present in normal animal or plant tissues; the more or less injurious consequences following the consumption of food into which formed mineral or organic poisons have been introduced by accident or with intent to improve appearances or keeping quality; the cases of infection due to the swallowing of bacteria and other parasites which infest or contaminate certain foods; and the poisoning due to deleterious substances produced in food by the growth of bacteria, molds and similar organisms. It is the purpose of this and the succeeding chapter to discuss those types of food poisoning which can be described as bacterial food infections and food intoxications.

The use of the term *bacterial food infection* is in itself misleading because, strictly speaking, it should include all instances where bacterial infection is transmitted through the medium of food. This would include many cases of typhoid fever, tuberculosis, anthrax, streptococcus and various other infections, but these are usually spoken of as food-borne infections, whereas usage has restricted the term *food infection* to include only that group of acute gastro-intestinal infections which is caused by the paratyphoid-enteriditis group of bacteria. The symptoms which are produced by these bacteria are very characteristic and are always produced by the ingestion of contaminated food.

Incidence.—The incidence of food infections in the United States is not known since, with the exception of botulism which is reportable in a few states, food poisoning is not a reportable disease in this country. It is impossible to establish the diagnosis without extensive laboratory investigations, and, in the great majority of instances, no laboratory studies have been made. Jordan, during a period of two years, collected, through the press-clipping bureaus and other sources, records of 375 group and family outbreaks, which were said to be food poisoning, in which 5,238 persons were involved, and he concluded that probably several thousand outbreaks occurred in the United States during a year.

It must not be forgotten, however, that many cases which are alleged to be cases of food poisoning are, in fact, not correctly diagnosed. Geiger has recently investigated 147 outbreaks of alleged food poisoning in which 1,578 persons had been involved, and he found that in 113 outbreaks there was no evidence that the illness had been food poisoning, but that the facts pointed to other diseases and conditions. In these outbreaks 85 persons died, of which only 4 were examined postmortem, and in 3 of the 4 cases "the original diagnoses (food poisoning) were completely refuted or changed."

It is highly desirable that greater care be exercised in arriving at a diagnosis of food poisoning and that the use of the term *ptomaine poisoning,* which is too often synonymous with *not diagnosed,* should be eliminated from the list of possible diagnoses. When there is reason to believe that an outbreak of illness is food infection or food intoxication, the aid of a well-equipped laboratory should be enlisted and careful examinations from the laboratory as well as from the clinical and epidemiological aspects should be made before a definite diagnosis is reached. The laboratories of the state boards of health will always coöperate in the solution of these problems.

Etiology.—The first of the paratyphoid-enteriditis group of bacteria was isolated by Gaertner in 1888, at Frankenhausen in Germany, where more than fifty persons became ill after eating the flesh of a cow which had been slaughtered because it was suffering from dysentery. From the spleen of one young man who died and from the tissues and contents of the intestine of the cow, Gaertner isolated an organism which was pathogenic to certain animals and which he named Bacillus enteriditis. Since then there have been many outbreaks of food poisoning in various parts of Europe and Great Britain, and a few in the United States where the bacterial cause was shown to be an organism of the same general type.

There has been much discussion as to what bacteria should be included in the paratyphoid-enteriditis group and the question is by no means settled at the present time. Many bacteria of similar type, some of them pathogenic and others apparently non-pathogenic, have been recovered from the tissues or excreta of sick and normal animals and fowl of different species, and it is not yet known what relation, if any, exists between them.

All the members of the group have certain characteristics in common:

"They are all Gram-negative, short bacilli with rounded ends which do not form spores. The majority of them are motile. They ferment dextrose, maltose, mannite, xylose and rhamnose with the formation of acid and gas, but do not ferment lactose, saccharose, salicin, raffinose, dextrin nor inulin. They produce transient acidity in litmus milk but later give rise to a markedly alkaline reaction. They reduce neutral red but do not form indol nor liquefy gelatin." (Topley, Weir and Wilson.)

Final differentiation can only be accomplished by agglutination and absorption tests.

The majority of German investigators recognize but two subgroups in this large group of bacteria, one consisting of B. enteriditis and the other including B. paratyphosus β, B. aertrycke and B. suipestifer, all of which they believe to be identical; but many British and American authors agree that B. paratyphosus β and B. suipestifer can be differentiated by agglutination and absorption tests and describe three subgroups, B. enteriditis, B. paratyphosus β, and B. suipestifer. Some of the British authors do not believe that the true B. paratyphosus β is ever observed excepting in cases of paratyphoid fever which are very similar in their course to typhoid fever, but describe as B. aertrycke the organism which is the cause of many cases of food poisoning. The cultural characteristics of B. aertrycke are identical with those of paratyphosus β, but, according to Savage, they can be differentiated by agglutination and absorption tests.

The nomenclature of the various bacteria belonging to this group is, therefore, very confusing and much work remains to be done before the relationships of the various members of the group are understood. In a recent attempt to accomplish this result, Topley, Weir and Wilson, in a report to the Medical Research Council of Great Britain, conclude that the relation which exists between B. enteriditis (Gaertner) and many of the members of the paratyphoid and suipestifer groups is similar to that which exists between the seriologically differentiated subgroups of meningococcus and of pneumococcus.

There has also been much discussion as to whether the members of this group of bacteria form true toxins. One group of workers, chiefly German investigators, have described the occurrence of true soluble toxins in the filtrates of broth cultures; but other investigators, including British, French and some Germans, have been unable to demonstrate them. Ecker, in 1917, reviewed the whole subject and reported that, in cultures of some strains of B. paratyphosus β, he had been able to demonstrate toxic substances which resembled true toxins in that they produced constant pathological effects and stimulated the formation of specific antitoxins. More recently Rosenau has reported that Aronovitch, working in his laboratory, found that some strains of the enteriditis group produce subtances in the filtrate which are toxic to guinea pigs and mice when administered by subcutaneous injection, but that they are not even irritating when administered by mouth. The symptoms which are produced by injection, however, in no way resemble those which are characteristic of true food poisoning.

Some investigators believe that toxic substances are contained as endotoxins within the bacteria and that they are liberated when the bacteria are slightly heated, as in the less well-cooked portions of infected food, but this has not been fully established and is denied by others.

All observers who have described toxins in this group of bacteria are agreed that they are relatively resistant to heat and that they will remain potent after exposure to degrees of heat that will destroy the living bacteria.

It has been suggested that various other bacteria, B. proteus, B. fæcalis alcaligenes and even B. coli may be responsible for outbreaks of food infections, especially when the food is contaminated with enormous numbers of the bacteria, but the more recent investigations do not appear to support this supposition. The only bacteria which have been proved to be the cause of food infections of the type under discussion belong to the paratyphoid-enteriditis group.

Sources of Infection.—The majority of outbreaks of food infections of this type are produced by the consumption of foods of animal origin, particularly those obtained from hogs and cattle, although a few have been described where vegetable foods, fowl, fish and shellfish have been at fault. It has not been possible to draw any general conclusions concerning the source of infection from the outbreaks which have occurred in the United States because of the small number which have been thoroughly investigated, but larger groups of cases have been investigated in Great Britain and in Europe and from these certain outstanding facts have been established.

According to Savage, the great majority of outbreaks has been produced by the ingestion of meat or milk from diseased domestic animals or from animals which have survived an infection and are still carriers of virulent pathogenic bacteria. B. enteriditis is a common cause of dysentery in calves and of gastro-enteritis, mastitis and abscesses in cattle. Many cases are recorded where the infection with this organism has been definitely traced to the milk of cows which were suffering from B. enteriditis infection of the udder, and others to meat from cattle which were affected with gastro-enteritis or abscesses before they were slaughtered. So frequently has this been true that some public health authorities advocate that all susceptible animals should be observed by a veterinarian for several days, and should have their temperature recorded before they are passed as being fit for slaughter.

Some cases are recorded where meat obtained from animals which were apparently free from disease at the time they were slaughtered became contaminated with B. enteriditis before it was consumed and was the medium through which the infection was transmitted to those who ate it. Savage believes that these cases are unusual and does not agree with the German investigators who believe that normal animals may be carriers of the pathogenic bacteria. He suggests that the probable cause of contamination in these instances is through lack of cleanliness in the abattoir or through handling by persons who have recently been infected and are temporary carriers. O'Kelly has reported an enteriditis outbreak of considerable size where the infection was transmitted by milk which had been contaminated by an attendant who had recently suffered from a mild diarrhea.

B. suipestifer, which the Germans believe to be identical with B. paratyphosus β, is also a frequent cause of food infection in man, and is commonly encountered as a secondary invader in hogs which are suffering from hog cholera. The instances where food infection has been directly traced to hogs which were suffering from hog cholera are infrequent, but a considerable number of outbreaks in Great Britain have been shown to be due to infection with B. aertrycke, which is the name the British have given to B. suipestifer of human origin.

B. paratyphosus β, according to Savage, has never been observed except in persons suffering from food infections or in persons who have recently recovered from the infection and are temporary or chronic carriers. The source of contamination of foods with this organism, except through human carriers, has, therefore, not been demonstrated.

The importance of human carriers as spreaders of food infection has not been fully determined. Only in rare instances has B. enteriditis been encountered in human beings except in persons who were suffering from or had recently recovered from an enteriditis infection, and it is probable that human carriers play a very small part in the distribution of infection with this organism. B. paratyphosus β and B. aertrycke, on the other hand, have only been found in human beings, and it has been demonstrated that chronic carriers may remain an active menace for a considerable time after they have recovered from an infection.

There are very few instances in which there is evidence that the infection was transmitted directly from one person to another.

In practically all instances where infection has occurred, the food which was responsible had been insufficiently cooked. In Gaertner's original report, it is stated that 36 persons who ate only cooked meat or soup remained free from illness, and since then there have been many instances recorded where persons who ate the uncooked food became infected, whereas those who ate it after it had been cooked remained in good health.

There are instances, however, where left-over foods have been responsible for transmitting infection, although that portion of the food which was consumed when it was first prepared had not caused any illness. One possible explanation for this is that the raw food may have been contaminated, but during the process of cooking all but a few of the bacteria were destroyed, so that in the freshly prepared food there were so few living bacteria that the body was able to resist the invasion; in the interval which elapsed before the left-over food was eaten, however, the bacteria which survived the cooking had reproduced in such numbers that the food became highly infectious. Another explanation is that after the food was cooked it became contaminated through being handled by a human bacteria carrier or from contact with other contaminated food.

Seasonal Distribution.—The majority of outbreaks of food infection occur during the summer months when the higher temperature facilitates the rapid reproduction of the bacteria in the infected foods. This is the reverse of what is observed in botulism, which is a poisoning produced by spoilage in preserved foods and occurs with greatest frequency during the winter months when fresh foods are not so readily available.

Pathology.—There is no characteristic lesion by which infection with the paratyphoid-enteriditis group of bacteria may be identified, and the pathologic appearance of the tissues in fatal cases may be insignificant when compared with the severity of the symptoms of the patient before death. Nevertheless, necropsy should be performed in all fatal cases where food poisoning is suspected, in order that other demonstrable causes of death may be excluded or that the diagnosis of food infection may be established by bacteriologic examination of the tissues.

The most frequent demonstrable lesions of food infection are hyperemia and edema of the gastro-intestinal mucosa, punctate hemorrhages or ecchymoses in the walls of the tract, occasional sloughing and ulceration of the mucosa in more severe cases, hyperemia of the adjoining viscera and cloudy swelling of the liver and kidneys. The spleen is usually congested and may be enlarged.

Microscopic examination of the tissues may show cloudy swelling and desquamation of the epithelial structures of the mucosa and often round-cell infiltration and microscopic hemorrhages throughout the tissues.

Symptomatology.—The symptomatology of food infection is essentially that of a severe gastro-enteritis with nausea, vomiting, pains in the abdomen and diarrhea. The onset is usually sudden and occurs in from six to twelve hours after the contaminated food is eaten, although Savage records that in his series of outbreaks in Great Britain the time of onset varied from one-half to forty hours after the causative meal. Those authors who believe that a virulent toxin is produced by the bacteria of this group explain this marked variability in the incubation period of the illness by assuming that, in those instances where a quantity of toxin is ingested with the infected food, the onset of symptoms occurs early, whereas if but little or no toxin is present the symptoms are delayed until the bacteria can manufacture sufficient toxin within the body to cause the illness.

There is a wide variation in the severity of the symptoms in different outbreaks of the infection and among the different victims of a single outbreak, all degrees of illness being met with, from a mild nausea, with or without vomiting or diarrhea, which is so slight that the patient does not discontinue his work, to a severe gastro-enteritis, associated with signs of shock which results fatally within twenty-four or forty-eight hours.

Diarrhea is the most constant feature of the infection and is associated with cramplike pains and more or less tenderness in the abdomen. Occasionally the abdominal pain may be the first indication of illness. The diarrhea is severe and profuse; in the early stages the stools are offensive, but later they become more watery and of a greenish color. In severe cases they may contain fresh blood. Tenesmus is common and frequently severe.

Nausea and vomiting are less constant. In one of the large outbreaks in England, they were noted in 75 per cent of the cases, but usually they occur early and may be severe. In the more severe cases the vomiting may be persistent and the vomitus may contain blood. Excessive thirst is a constant symptom.

In some cases the onset of the gastro-intestinal symptoms may be preceded by headache and occasionally there may be an initial chill. Headache, dizziness, vertigo and depression are characteristic of the infection and in the more severe cases the patient is usually restless and apprehensive, often suffers from insomnia and may even be delirious. In the most severe cases, the patients show all the characteristics of traumatic shock and may pass into a state of coma before death. Many children and some adults have convulsions.

In the milder cases there may be no fever, but in well-marked cases a rise in temperature to from 100° to 103° F. is usually noted within a few hours after the onset of the illness, and in the more severe cases the temperature may rise as high as 105° F. Occasionally there may be rigors. The presence of fever is one of the earlier differential points in the diagnosis from botulinus intoxication.

The pulse in mild cases may not show much variation from normal, but in more severe cases it is common to observe a rate of from 100 to 120 or even to 160 per minute, depending upon the severity of the infection. In the most severe cases the pulse is identical with that observed in shock.

A most striking feature of the more severe infections is the extreme prostration of the victims. This appears early, is constant and usually persists for a long time, making convalescence slow and tedious. There may be cramplike pains in the muscles of the extremities.

The mouth is dry and parched, the tongue is coated and the breath is offensive. In severe cases with shock the body is bathed in cold sweat.

In some outbreaks, especially those in which the illness has been transmitted by fish or shellfish, there is a general erythema or urticaria, sometimes so severe as to result in desquamation. Herpes labialis has been described in a few instances.

The duration of the illness varies greatly, depending upon the severity of the infection and the identity of the infecting organism. In the mildest cases the patient may be practically well, except perhaps for some weakness, within twenty-four hours after the onset of his illness, but in the most severe cases there may be a fatal termination within twenty-four to forty-eight hours. In the majority of instances, however, the febrile stage persists for not longer than one to three days and the patient gradually recovers his strength. Occasionally, when B. paratyphosus β is the infecting organism, the illness may be protracted and run a course which is practically identical with typhoid fever.

Recovery is often complete, but not infrequently a gastro-intestinal irritability persists which may become chronic. In some instances there appears to be a peculiar hypersensitiveness to spoiled foods which may last for years.

Mortality.—Reliable mortality statistics are not available in the United States because of the limited number of instances in which complete investigations have been recorded; but Savage reports that in the outbreaks in Great Britain, in which bacteria of the paratyphoid-enteriditis group are known to have been the cause, the case mortality rate was 1.47 per cent. The mortality rate in Great Britain is very similar to that reported by Mayer in the German literature.

Diagnosis.—The diagnosis of bacterial food infections and the recognition of the food which is at fault may be attended with considerable difficulty. When a number of persons who have dined together or who have partaken of some common article of diet are all seized with nausea, vomiting and diarrhea, there is strong indication that food poisoning is the cause of their illness and it is usually not difficult to form some conclusion as to what particular food was responsible. When only one person becomes ill, however, particularly if he has not partaken of food other than that consumed by other people, great care should be exercised in arriving at a diagnosis and food infection should not be diagnosed until all other possibilities have been excluded.

Sudden onset of nausea and vomiting associated with cramps in the abdomen, more or less fever and prostration, occurring within a few hours after the ingestion of food, is not pathognomonic of bacterial food infection. Any acute abdominal condition, appendicitis, cholecystitis, cholelithiasis, gastric ulcer, etc., certain chest conditions, pleurisy or angina pectoris and other acute infections may produce symptoms of a similar nature and must be excluded. Harris believes that the occurrence of constipation instead of diarrhea may be taken as a mark of differentiation between these conditions and food poisoning, but that cannot be taken as absolute because early and persistent constipation is characteristic of many cases of botulism.

In all cases where food infection is suspected, laboratory assistance should be obtained and a diagnosis of food poisoning should not be made unless the characteristic laboratory findings can be established.

Treatment.—Food infection is a disease of limited duration and the case mortality rate is very low. It is essential, however, that the patients be kept in bed and as quiet as possible. The administration of opium or any of its derivatives in the early stages of the infection is contra-indicated, except in those cases where the symptoms of shock must be combated, because it is necessary to eliminate the infected food from stomach and intestines as soon and as thoroughly as possible. After elimination has been accomplished, symptomatic and supportive treatment are indicated.

Regardless of whether the patient has vomited freely, the stomach should be emptied and thoroughly washed at the earliest possible moment, to eliminate all portions of the infected food which may remain. The method of choice is to pass a large stomach tube in which several openings near the end and the lumen are large enough to permit the passage of particles of food, and to wash and rewash with warm water until the return is free from any food remnants. Some authors prefer the addition of boric acid, 1 tablespoonful to the gallon, because of its antiseptic action, and others recommend sodium bichlorid, 2 heaping tablespoonfuls to the gallon, but the most important thing is to continue lavage until the stomach has been completely emptied.

In case a stomach tube is not available or where, because of persistent retching, it is difficult to retain it in position, copious draughts of lukewarm water which contains sodium bicarbonate or sodium chlorid may be given to induce vomiting, and should be repeated until all particles of food have been removed from the stomach. Apomorphin or the usual emetics, ipecac, mustard water, tartar emetic, etc., may be given, but are not to be preferred, because it is the thorough washing of the stomach which is desired.

The bowel should also be cleansed as thoroughly as possible, even though there has been free diarrhea. This may be accomplished by the administration of oleum ricini or magnesium sulphate, and by the administration of large enemata of warm water, frequently repeated. When gastric lavage has been completed, the oleum ricini, ℥ss to ℥i, or magnesium sulphate, ℥ss to ℥i in saturated solution, may be passed into the stomach through the stomach tube before it is withdrawn. By many clinicians, castor oil is preferred to Epsom salts because of its secondary sedative effect upon the intestine.

Some authors recommend the administration of calomel in divided doses, gr. 1/10 every 15 minutes until ½ to 1 gr. has been given, to be followed in 4 or 5 hours by a mild saline, but this requires a considerably longer time to be effectual and for that reason the castor oil or Epsom salts is to be preferred. *It is important that no laxative should be administered by mouth until after the stomach has been thoroughly washed.*

The application of a mustard plaster, 1 part mustard in 4 of flour, or of an ice-bag over the epigastrium will often give relief from persistent nausea, and a larger mustard plaster over the whole abdomen, turpentine stupes or a hot-water bottle may aid in controlling abdominal pain. Nausea and vomiting often yield to the administration of bland liquids, such as barley water or albumen water, given in small quantities at frequent intervals, 1 teaspoonful every 15 minutes or ½ hour.

It should again be emphasized that the administration of opium or any of its derivatives in the early stages of the disease is distinctly contraindicated. Elimination of the infected food is essential, and, until the bowels have been thoroughly cleansed, opiates should not be given.

Diarrhea may cease when the bowels are thoroughly evacuated, but not infrequently it persists and is difficult to control. Bismuth subnitrate or subgallate, gr. xv every 1 or 2 hours, may give relief, but if these fail the addition of 1 teaspoonful of tincture opii camphorata every hour will usually control it. Some authors advise the administration of salol, gr. v every 4 hours, as an aid in intestinal antisepsis.

Distressing thirst is a constant feature of the more severe cases of food infections, and is indicative of partial dehydration of the tissues. It is possible that in milder cases sufficient fluid may be taken by mouth or that the Murphy drip may be tolerated, but in more severe cases neither method of administration of fluids is available. Cracked ice does not usually induce vomiting, and may be given freely, but in the more severe cases it is impossible to administer sufficient fluid except by intravenous injection of normal salt solution or by hypodermoclysis.

In severe cases the usual symptoms of shock may be encountered, and these should be treated as one would treat traumatic shock. The patient must be kept warm, wrapped in blankets with hot-water bottles to the extremities, and fluids should be administered by mouth or by colonic irrigation if they can be retained, or by hypodermoclysis or intravenous injection of normal saline. If the intravenous route is employed, the fluid should be injected slowly.

Caffein is the stimulant of choice in these cases. If the patient can retain it, hot, strong, black coffee may be the medium of administration, since this combines internal heat, fluid and stimulant; but, if it cannot be given in this way, caffein citrate, gr. ii, by hypodermatic injection, should be given and repeated as necessary. Camphor in oil by hypodermatic injection or ether may be used in emergency, but these are not to be preferred to caffein. Strychnin has been recommended by some authors but it is preferable for use during convalescence.

Gastric lavage and colon irrigation with warm water are even more important in cases showing signs of shock, especially if it has been necessary to administer opiates, since they then constitute the most important methods of elimination, as well as aid in maintaining warmth by the application of the heat internally.

No solid food should be allowed until the acute stage of the infection is well over. Barley water or thin gruel is well tolerated, but it has been suggested by some authors that milk should not be given as it is so excellent a medium for bacterial growth. Return to solid food should be very gradual. In some instances there seems to be a late inhibition of gastric secretion so that dilute hydrochloric acid in the usual dosage and well diluted in water should be given after meals.

Prophylaxis.—The prevention of food infections is a problem with which the public health authorities are vitally concerned. The regulations dealing with the cleanliness and care of foods which are to be sold, the government inspection of abattoirs and of slaughtered animals, and the supervision of dairy products control to a very great extent the danger of infection from meats, fish, milk, butter and other foods which are offered for sale. The greatest danger lies in foods which are prepared at home by persons who do not understand the dangers of food poisoning. No animals should be slaughtered for food unless they are perfectly healthy, and any food which shows any signs of spoilage should be discarded.

It must be remembered, however, that food may be contaminated with bacteria of the food infection group without showing any signs of spoilage, and the surest method of prevention is to cook thoroughly all susceptible foods before they are eaten.

Although it is not required by law that all cases of suspected food infection should be reported, in the interest of prevention of further outbreaks, the health authorities should be informed, in order that steps may be taken, first, to establish diagnosis, and, second, to prevent further distribution of food which may be the cause of the infection.

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CHAPTER XVII

BACTERIAL FOOD INTOXICATION OR BOTULISM

Ernest C. Dickson

Botulism is not a food infection but a food intoxication, and is the only type of food poisoning in which a bacterial toxin has been proved to be the cause of the illness. The toxin is produced by the growth of Clostridium botulinum in preserved food and is taken into the stomach in its fully toxic state when the contaminated food is ingested. It may produce characteristic symptoms in various types of animals and birds as well as in man and is a cause of forage poisoning in domestic animals, particularly horses and mules, and of fowl botulism (limber neck) in domestic fowl.

Incidence.—Botulism is not a new disease, but has been recognized in various parts of Europe since early in the nineteenth century. In the early German literature the term was used synonymously with Wurstvergiftung (botulus is the Latin word for sausage), but gradually it became known that identical intoxication may be produced by spoiled preserved meats, other than sausage, and fish, and in more recent European literature it has been applied to poisoning produced by any of these food products.

The majority of recorded outbreaks in Europe have been described in Germany and Austria, but outbreaks have occurred in Switzerland, Hungary, Russia, Belgium, Holland, Denmark and France. A single outbreak has been described in England within the past few months.

The incidence in the United States and Canada is not known, because until 1902 no outbreak in this country was differentiated from "ptomaine poisoning," and because until recent years there has been no attempt to make food poisoning a reportable disease in any of the states or provinces. Since 1914, however, there has been more active interest in the subject, and reports of all outbreaks that could be traced are now recorded.

These records show that in the United States and Canada, between 1889 and 1922, there have been 107 reported outbreaks of botulism affecting human beings in which 380 persons were poisoned, and at least 53 more in which domestic animals or fowl were poisoned by eating food which had been prepared for human consumption but was discarded because it had spoiled. The greatest number of recorded outbreaks has been observed in the Pacific Coast states, where, since 1916, a most careful investigation has been made in every instance where it was learned that illness of human beings or animals was suspected to be due to food poisoning.

Prior to 1914, in all instances where botulism was diagnosed in this country, the diagnosis was based entirely upon the clinical manifestations of the victims, but since that time the majority of outbreaks have been carefully investigated from the laboratory as well as from the clinical point of view and many instances are now recorded where the diagnosis was established by the demonstration of Clostridium botulinum or its toxin.

Etiology.—The actual cause of botulinus intoxication was discovered by Van Ermengem in 1894, when he investigated an outbreak of botulism which occurred at Ellezelles in Belgium, in which 23 persons became ill and 3 died after eating ham which had been preserved in brine. Van Ermengem demonstrated that the poisoning was due to the presence of a toxin in the ham and that the toxin had been formed by the growth of an anaërobic bacterium which he called Bacillus botulinus. His observations have been confirmed by many investigators and it is now known that this bacterium is always responsible when food poisoning of the botulinus type is encountered in human beings or in animals.

Clostridium botulinum.—Clostridium botulinum is an anaërobic, spore-bearing, toxin-producing organism which is widely distributed in nature, and is one of the many bacteria of the soil whose normal function is not known. It occurs in large numbers in virgin soil from the tops of mountains as well as in the cultivated soil of valleys and apparently is independent of animal life for its propagation. It has been demonstrated in practically all portions of the United States and in many parts of Canada, Great Britain, Europe and the Hawaiian Islands.

It is usually classed as anaërobic, but is not strictly so. It grows abundantly in mediums which are only partially anaërobic, and it is frequently encountered in haystacks, ensilage, etc., in symbiotic association with vigorous aërobic forms of bacteria and yeasts.

Subterminal spores are formed in enormous numbers when conditions are favorable for rapid growth of the bacteria. The majority of them germinate promptly when placed in favorable environment, but a small percentage in many cultures possess a dormancy which is analogous to that observed in seeds, and may show no signs of growth for at least five months after they have been placed in suitable mediums under ideal laboratory conditions. Despite this delay in germination, the resulting bacterial growth is apparently identical in vigor and in toxin-producing power with those which develop from spores which have germinated promptly.

There is also marked variation in the resistance of the spores to heat, the variation being shown between the spores of different strains of the organism and also between individual spores of a culture of a single strain. The great majority of the spores, more than 95 per cent, are not especially resistant to heat, but in many cultures there are some spores which are much more highly resistant and a few which may be termed extremely resistant to heat. The maximum survival times which have been established by laboratory tests are: six hours' exposure to the temperature of boiling water; ten minutes to 115.5° C.; and six minutes to 121° C. There is a considerable increase in the time required to destroy the spores at any given temperature if there is a thin layer of oil on the surface of the liquid in which the spores are heated.

The dormancy which occurs in normal unheated spores is greatly increased in those which have survived exposure to heat, and in laboratory tests delayed germination has been observed for more than two years after the spores were heated. The bacterial growths which resulted from the germination of these dormant spores are apparently as vigorous as the parent cultures and produce as virulent a toxin as was obtained from the original cultures before the spores were heated.

Botulinus Toxin.—Botulinus toxin is a true bacterial toxin which differs from tetanus and diphtheria toxins by being unaffected by gastric digestion. It can be obtained in dried form by precipitation with neutral salts, and is also precipitated by alcohol or tannin. It has been suggested that the consumption of alcoholic beverages with poisonous food will lessen the possibility of poisoning with the toxin, but the evidence in an outbreak where the botulinus intoxication was transmitted by home-brew, in which there was approximately 15 per cent alcohol, throws considerable doubt upon this assumption.

The toxin is extremely virulent for human beings as well as for certain animals and fowl, and the mere tasting of contaminated food "to see whether it was spoiled" has been responsible for the fatal intoxication of several housewives. The avenue of entrance of the toxin into the body, by mouth or by subcutaneous, intramuscular, intravenous or intradural injection, does not affect the character of the symptoms which are produced in animals under experimental conditions, although the rapidity of onset varies with the method of administration. An ordinarily vigorous strain of Clostridium botulinum, when grown for from five to ten days in suitable medium, will produce toxin of such strength that 0.0001 c.c. of the filtered broth by subcutaneous injection will kill a guinea pig within two days.

The botulinus toxin is easily destroyed by heat, and numbers of instances are recorded where persons who ate portions of uncooked contaminated food developed the typical symptoms of botulism, whereas others who ate portions of the same food after it had been cooked were not poisoned. The degree of heat and the time necessary to destroy the toxin varies according to the character, consistency, etc., of the food in which it is contained, and under laboratory conditions there appears to be a greater heat resistance when the toxin is in vegetable medium than when it is in broth. The maximum resistance time that has been recorded under laboratory conditions is twenty minutes' boiling in spinach juice, but usually the toxin is destroyed by boiling for from five to seven minutes.

Antitoxin.—Specific antitoxin is produced when suitable animals are gradually immunized to botulinus toxin over a period of several months. By toxin-antitoxin tests it has been found that there are two distinct types of Clostridium botulinum, which have been called A and B. Each type of the organism is serologically distinct, the toxin of each is completely neutralized by its homologous antitoxin, but the virulence of Toxin A is not reduced by Antitoxin B, nor is Toxin B affected by Antitoxin A. It has been suggested that the two types may be differentiated without the toxin-antitoxin tests by feeding chickens with the suspected food, because of a supposition that chickens are not susceptible to Toxin B. It is true that chickens do appear to be less easily poisoned by Toxin B than by Toxin A, but cases are recorded in which large numbers of chickens have succumbed to poisoning with spoiled home-canned food which was contaminated with Toxin B.

There has been considerable discussion as to whether Clostridium botulinum can act as a true infecting organism and produce sufficient toxin within the body to cause signs of poisoning. Under experimental conditions it has been shown that guinea pigs will die after the administration of massive doses of detoxified spores by mouth or by subcutaneous injection, but there are no records that human beings have acquired symptoms of botulism unless they have ingested the toxin.

Sources of Intoxication.—There is a very striking difference between the types of foods which are responsible for the recorded outbreaks of botulism in Europe and in America. In Germany, where botulism has been recognized for more than a century and where food poisoning has been a reportable disease for many years, only 3 outbreaks have been attributed to foods of vegetable origin, canned beans, the other outbreaks being all attributed to foods of animal (including fish and fowl) origin. In other parts of Europe and in Great Britain, all known outbreaks have been attributed to foods of animal origin.

In the United States and Canada, there have been 97 outbreaks of botulism affecting human beings and 53 in which domestic animals or fowl were poisoned by eating spoiled food which had been prepared for human consumption (Table I). Of these 150 instances of botulinus poisoning, 127, 84.6 per cent, were caused by the consumption of preserved vegetables or fruits, and only 25.4 per cent were caused by preserved foods of animal origin.

It is probable that this great difference in the direct cause of the poisoning in the two continents is dependent in part upon different habits of diet. In those portions of Europe where botulism is most common, it is the custom to eat smoked sausages and other preserved meat products without further cooking, whereas in the United States the meats are usually cooked, but preserved vegetables and fruits are frequently served directly from the container, as salad, relish or dessert.

The majority of outbreaks in this country, both of those affecting human beings and those affecting fowl, have been caused by the consumption of home-canned products. Of the total 150 outbreaks recorded in Table I, 113, 75.6 per cent, were attributed to home-canned products, and of the 97 outbreaks in which human beings were poisoned, in 62, 63.9 per cent, home-canned products were believed to be at fault.

In approximately one-third of human outbreaks in this country, the diagnosis was established by laboratory methods, in the others the causative food was recognized by epidemiological investigation.

TABLE I—FOODS BELIEVED TO HAVE BEEN RESPONSIBLE FOR OUTBREAKS OF BOTULISM IN THE UNITED STATES

	Home-Canned Products		Commercially Canned Products		Total
	Human Beings	Domestic Fowl and Animals	Human Beings	Domestic Fowl and Animals	
String Beans	21	23	3		47
Corn	12	17	2		31
Spinach	3		8	1	12
Peas		4			4
Asparagus	6	4			10
Beets	1		2		3
Olives			11		11
Apricots	3				3
Pears	2				2
Tomato Products	1 (49)	1 (49)	1 (27)	1 (2)	4 (127)
Pork Products	5		4		9
Beef Products	3				3
Sea Food	2	1	3		6
Dairy Products	2		1		3
Chicken	1 (13)	1 (2)	(8)		2 (23)
Total	62	51	35	2	150

H.C. Products, 113; C.C. Products, 37; Vegetable foods, 127; Meat foods, 23

Seasonal Distribution.—The majority of outbreaks of botulism occur during the winter months when fresh foods are not so readily available, but, as preserved foods form so large a portion of our staple diet at all seasons, particularly in cities, outbreaks may be encountered at any time.

Pathology.—There is no characteristic gross lesion by which botulism can be recognized at necropsy. There is marked congestion of the central nervous system and of the abdominal and thoracic viscera and there may be multiple hemorrhages around the base of the brain and upper part of the cord and in the brain tissue. Frequently the lungs show areas of bronchopneumonia. All the parenchymatous organs show cloudy swelling and the heart muscle is weak and flabby.

On microscopic examination all the tissues show marked congestion and often there are perivascular hemorrhages, particularly in the brain and meninges. Cellular thrombi are usually observed in the blood-vessels in different parts of the body, but they may not occur when the duration of the illness has been short, and are not to be considered pathognomonic of botulism. In none of the cases studied in this country has there been any indication of ganglion cell destruction such as has been described by European investigators.

Recent experiments have shown that the botulinus toxin acts peripherally upon the nerves of certain portions of the nervous system, and not centrally upon the ganglion cells of the brain or of the cord. The most marked effect occurs in the parasympathetic fibers of the third, seventh, tenth and eleventh cranial nerves, and of the pelvic nerve, which constitute that portion of the autonomic nervous system which Gaskell described as the prenuclear and bulbosacral outflows. In these nerves there is a blocking of nerve impulse which is not due to an organic destruction of the nerve structure, but the effect of the blocking is such that true paralysis is simulated.

The action upon the skeletal motor nerves is less severe, since initial normal nerve stimuli result in normal maximum contractions of the muscles. There is, however, a very early and very extreme fatiguing of the muscle when repeated stimulations are received, the fatigue being apparently due to some disturbance in the mechanism for transmitting the impulse for contraction, and not due to any change in the muscle cell itself.

There is no demonstrable effect upon the blood-pressure regulating mechanism or upon any of the other functions of the true sympathetic system which Gaskell described as the thoracicolumbar outflow of the autonomic nervous system.

Symptomatology and Course.—Botulism differs from the usual types of food poisoning in that it is characterized by delayed onset, absence of or relatively mild gastro-intestinal symptoms and involvement of the nervous system associated with disturbances of vision, difficulty in swallowing and in talking, persistent constipation, extreme muscular weakness, subnormal temperature and rapid pulse.

The early diagnosis is frequently rendered difficult by the fact that in about one-third of the cases there is an initial gastro-intestinal disturbance with nausea, vomiting and diarrhea, which may begin within from two to four hours after the spoiled food is eaten and may last for from twelve to thirty-six hours later when the true botulism symptoms set in. This gastro-intestinal disturbance is probably caused by the local irritating effect of the spoiled food and is not a part of the botulism syndrome. Usually when symptoms occur very early they are of this gastro-intestinal type.

The onset of the typical symptoms of botulism is usually delayed for from eighteen to thirty-six hours after the poison is ingested, and may not appear for several days. In a series of 213 cases, the initial symptoms occurred within forty-eight hours in 74 per cent, and the longest incubation period was eight days. In general it may be stated that the rapidity of onset of illness depends upon the intensity of the intoxication, and that, when the time of onset is much delayed, the illness of the victim is less severe.

The earliest indication of illness in the majority of cases is an indefinite lassitude, sometimes associated with headache and dizziness and constipation, or it may be a disturbance of vision, with scintillations, and dimness of vision due to partial loss of accommodation for near vision, or even double vision. Occasionally, even when acute gastro-intestinal disturbances are lacking, the patient complains of burning and distress in the region of the stomach.

Disturbances of vision occur early and are very constant. Involvement of the parasympathetic fibers of the oculomotor nerve results in mydriasis and loss of accommodation to light, and the development of fatigue of the extrinsic muscles of the eyes results in diplopia and blepharoptosis. Occasionally the pupils may be irregular in contour and unequal. Complete loss of accommodation soon follows. Nystagmus, sometimes unilateral, and photophobia have been described. The majority of observers agree that there is no lesion in the retina and that the patient has clear vision for distant objects when either eye is used alone.

The patients soon complain of a sensation of constriction in the throat and of difficulty in swallowing and in talking. The tongue is heavily coated on the surface, moves sluggishly and appears to be too large for the mouth. There may be complete loss of pharyngeal reflex. The voice is low in tone, and attempts at speech cause rapid fatigue, with progressive huskiness and retarded enunciation. Complete aphonia soon follows.

The difficulty in swallowing is apparently largely due to impaired action of the pharyngeal muscles as the patients state that if they can once get the food started they can easily swallow. In mild cases the solid food may be washed down by taking a drink of liquid with each mouthful, but in more severe cases this is impossible because of strangling and regurgitation of the fluids through the nose.

The strangling spells are most distressing and may persist until the patient is exhausted. They are frequently induced by attempts to swallow or to clear the pharynx of thick tenacious mucus, and are particularly dangerous because they may cause insufflation of the food or mucus into the trachea and bronchi, and thus induce bronchopneumonia.

There is early inhibition of the movements of the gastro-intestinal tract and cases are recorded in which remnants of the food which caused the poisoning were found in the stomach after death two or three days later. Constipation is a constant manifestation of the intoxication and is most persistent. There may be some accumulation of gas within the intestines, but effective peristalsis is completely lacking.

General muscular weakness may be so extreme as to simulate paralysis, but, although there may be ataxic gait and incoördination of muscular movements, the skeletal muscle reflexes remain intact. Under experimental conditions in animals, the weakness does not appear to be due to actual loss of muscular strength, but to excessive muscular fatigue, somewhat analogous to that seen in myasthenia gravis; and clinically in human cases it is often noted that the patient can open the eyes or raise the head or an extremity from the bed once or twice but cannot repeat the act. There is no evidence of rapid wasting of the muscles such as occurs in acute poliomyelitis.

Botulinus intoxication is also characterized by an almost complete absence of sensory disturbances, and mentality usually remains clear throughout the illness. There may be restlessness and anxiety with insomnia and sometimes hysteria, particularly in the early stages, but often the patient becomes somnolent and apathetic as the intoxication progresses. There may be spells of extreme irritability, especially when he is aroused, or when he is unable to make himself understood or to swallow. In a few cases there is coma for some time before death.

Inhibition of secretions is also characteristic of botulism, and the patients complain bitterly of dryness of the mouth and of thick tenacious mucus in the pharynx. There is often a more or less profuse sweat which has an offensive odor.

The temperature is normal or subnormal in uncomplicated cases, and this is one of the important points of differential diagnosis. When fever occurs it indicates some complication, usually bronchopneumonia.

The pulse may be slow in the early stages, but soon it becomes rapid, from 100 to 160 per minute, depending upon the severity of the intoxication. The combination of subnormal temperature with this high pulse rate is most striking.

As the intensity of the intoxication progresses, respiration becomes difficult and labored, and death usually results from respiratory failure. There may be Cheyne-Stokes' respiration in some cases.

There is nothing of diagnostic significance in the results of the usual laboratory examinations. The red blood count may be slightly higher than normal because of relative dehydration of the body when the patient is unable to swallow liquids, and the leukocyte count may be normal or it may vary from 10,000 to 15,000 per c.mm. The amount of urine is dependent upon the amount of fluid intake, but nothing that is characteristic is found upon examination. Nothing abnormal has been detected in the cerebrospinal fluid, and the blood-pressure lies within normal limits.

The duration of the illness varies greatly although the majority of the victims who die do not survive longer than from three to six days after the poisonous food is eaten. In 173 fatal cases where data are available, 18 died within forty-eight hours and 117 in from three to six days after ingesting the poison, whereas only 1 victim survived for longer than fifteen days. In general it may be stated that, if the patient survives for eight or ten days, he will recover unless death results from some complication such as insufflation bronchopneumonia.

Death usually occurs from respiratory failure and the heart may continue to beat for some minutes after respiration ceases. Cases are recorded where cardiac action persisted vigorously during several hours of artificial respiration. Not infrequently there is a terminal asphyxia and cyanosis, sometimes induced by the onset of a strangling spell. In some instances there is apparent improvement in the signs of the intoxication, but the patient later succumbs to the bronchopneumonia.

When recovery occurs, convalescence is extremely slow and tedious. The strangling and difficulty in talking and in swallowing are the first manifestation of the poisoning to disappear, but the general muscular weakness, including the disturbances of vision, may persist for weeks. During convalescence the blood-pressure may be considerably lower than normal, and it may be months before the patient regains his full strength. It is very seldom that persons who survive the poisoning suffer from any permanent disability.

Morbidity and Mortality.—Botulism is of relatively slight importance as a cause of illness among human beings, since from 1889 to 1922 all available records show that there have only been 106 recorded outbreaks in the United States and Canada.

The case mortality rate, however, is very high, 63.9 per cent. There is very marked variation in the mortality rate of different outbreaks, ranging from zero to 100 per cent, and there appears to be a general relationship between the amount of toxin ingested, the time of onset of symptoms and the number of the victims who succumb. Initial vomiting and diarrhea does not appear to play any part in alleviating the severity of the intoxication, as the mortality among those who had initial vomiting and diarrhea has been as high as among those in whom there was no initial acute gastro-intestinal disturbance.

Diagnosis.—There is little difficulty in making a diagnosis of botulism when a group of persons develop the typical symptoms within from twenty-four to thirty-six hours after having partaken of food together, particularly if it has been noted that some article of preserved food has shown signs of spoilage. When single cases are seen, however, the diagnosis may be much more difficult, unless, as is often the case, the victim of the poisoning remembers that he or she consumed some portion of preserved food which was not good. A relatively frequent history is that a housewife opens a jar of home-canned food and tastes it to determine whether it is good, and in rural districts it is not uncommon to note that numbers of chickens have developed "limber neck" after eating portions of discarded spoiled home-canned food. The incidence of this fowl botulism in some instances may give a clue to the cause of the illness of persons who may have tasted the food before it was discarded.

It should be remembered that the symptoms of botulism do not develop for from eighteen to thirty-six hours or even longer after the poison is ingested, and, when searching for a history of the consumption of spoiled food, a careful interrogation should be made concerning all the foods which have been consumed or tasted for at least forty-eight to seventy-two hours before the first indication of illness was noted.

In some instances in which it is evident that the victims are suffering from food poisoning, there may be difficulty in determining whether bacterial food infection or food intoxication is at fault, because, in a considerable proportion of cases of botulinus intoxication, there is initial nausea, vomiting and diarrhea. The continued absence of fever should arouse suspicion that bacterial infection is not responsible, and the first indication of disturbances of vision or of swallowing should suggest the diagnosis of botulism. Moreover, from the history it may be possible to arrive at some conclusion, because in food infection the cause of the illness is usually infected fresh food which probably does not show any signs of spoilage, whereas in botulism it is always contaminated preserved food which has not been thoroughly cooked before it was eaten and which usually shows some indications of spoilage. It is important that the diagnosis be made at the earliest possible moment, since the specific antitoxins are of no value in therapy unless they can be given very early in the course of the disease.

Epidemic encephalitis may be confused with botulism, particularly when there are diplopia and signs of bulbar paralysis; but here again the early rise in temperature should arouse suspicion and the cell content of the cerebrospinal fluid should aid in diagnosis.

Cerebrospinal syphilis and acute poliomyelitis must be considered, but the course of the disease soon establishes differentiation. There is seldom any difficulty in differentiating between botulism and methyl alcohol poisoning.

The symptoms of belladonna poisoning are very similar to those of botulinus intoxication and there may be difficulty in differentiating between them. The characteristic excitement and delirium of belladonna poisoning is not, however, usually observed in botulism, and a careful history will often reveal a possible source of poisoning.

It has been suggested by several authors that the botulinus toxin may be demonstrated in the blood serum of persons who are suffering from botulism, particularly in the early stages of the intoxication. White mice are particularly susceptible to the toxin and the test is made by injecting 1 c.c. of the patient's serum into the peritoneal cavity of the white mouse. It is said that the animals develop typical symptoms of botulism and die within a few hours.

A diagnosis can be definitely established within from twelve to twenty-four hours if portions of the poisonous food are available for examination. A small amount, 1 c.c. of the liquid from the food, or of a saline infusion of the solid portions of the food, should be injected into the peritoneal cavity of a white mouse or a guinea pig, or into the vein of a small rabbit. When botulinus toxin is present, the animal will develop typical signs of botulism within a few hours. If botulinus antitoxin is available, controls should always be made by injecting three animals, one with the suspected material alone, and one each with the suspected material and Antitoxin A and Antitoxin B respectively, in order to determine the type of the toxin as well as to establish diagnosis.

Treatment.—The high case mortality of botulism is evidence that the known methods of treatment are not satisfactory. It should be borne in mind, however, that the illness is caused by a limited amount of toxin and that, if the patient can be supported until its action has been exhausted, complete recovery follows. It was recorded by Müller in 1869 that few persons die who have survived the poisoning for ten days, and more recent reports have confirmed this observation.

The one most important thing in the treatment of botulism is that the patient be put to bed as soon as possible and kept as quiet as possible. Experiments have shown that fatigue of the muscles is a characteristic effect of the toxin and that it is from fatigue and not from paralysis of the respiratory muscles that death ensues. It has been noted in experiments on monkeys that if animals which can still sit up are taken from the cage and handled to the extent necessary to give intravenous injections of antitoxin, they may succumb almost immediately, and in clinical records there have been instances where the effort induced by moving a patient in an ambulance to the hospital has resulted in cessation of the respiratory function. Bronfenbrenner and Weiss noted that if guinea pigs were kept under ether anesthesia during the course of the intoxication the mortality rate was much diminished. They suggested that human victims of botulism should be anesthetized to conserve their strength until the antitoxin has time to neutralize the toxin in the body, but because of the respiratory distress in human botulism this has not proved to be clinically practicable. They also suggested that morphin be given with the antitoxin to produce the same effect, but the efficacy of this method has not yet been established.

The patient should be put to bed, preferably in a darkened room by himself, and kept free from all disturbing influences of any character. If restless or unable to sleep, he should be given bromids in full doses if he can swallow, or morphin *without atropin* by subcutaneous injection if it is necessary. He should not be disturbed by examination or encouraged to try to talk or swallow or do anything which will tend to cause fatigue.

When seen early in the course of the intoxication, before the difficulty in swallowing or the strangling spells have set in, the stomach should be washed to remove as much of the toxin as is possible, but in severe cases it is doubtful whether the benefit to be derived in this way is of sufficient value to offset the fatigue which the treatment must induce. I have seen one patient thrown into a strangling spell and die when attempts were being made to pass a stomach tube to perform lavage.

If the stomach can be emptied by lavage, full doses of magnesium sulphate or oleum ricini should be placed within the stomach before the tube is withdrawn. It is not advisable to induce vomiting with apomorphin or to attempt to give emetics if there is difficulty in swallowing or if the patient strangles, because of the danger of aspirating vomitus into the bronchial tree.

The colon should be thoroughly flushed with high enemata even though there has been initial diarrhea. Simple soapsuds enemata should be repeatedly given, but not persisted in to the extent that the patient is fatigued.

Simple nourishing food should be given if the patient can swallow or will tolerate the stomach tube, but care should always be exercised to avoid anything which will induce the strangling spells. Water should be given freely, and, because of the inactivity of the gastro-intestinal tract, retention enemata of normal salt solution or the Murphy drip are the methods of choice for its administration.

Supporting treatment should be applied as indicated. Caffein citrate, gr. 2 by hypodermic injection, or hypodermic preparations of digitalis may be tried for cardiac distress, but the onset of the cardiac distress is usually terminal and is not responsive to treatment. Strychnin has long been used and appears to be beneficial. It should be given in full doses, gr. 1/30 every four hours, so long as signs of muscle irritability are not produced. *Atropin, which is so useful in those types of food poisoning where there is gastro-intestinal irritability, is definitely contra-indicated* because the effect of the action of the botulinus toxin is in many ways identical with that produced by toxic doses of belladonna.

There is experimental evidence that the action of the botulinus toxin is counteracted by pilocarpin and Pelzl stated that 20 drops of a 1 per cent solution could be given daily without producing toxic symptoms. It should be remembered, however, that the patient is unable to cough because of the pharyngeal pseudoparalysis, and cases are recorded where the administration of pilocarpin has resulted in pulmonary edema which hastened death.

One of the most distressing features of the intoxication is the collection of thick, tenacious mucus in the pharynx which the patient is unable to cough up, and which often leads to severe strangling spells. This should be removed as often as is necessary by a soft swab on the end of a wooden spatula or handle of a teaspoon, or, better, through a soft rubber catheter which is attached to an aspirating bottle in which a slight negative pressure is maintained as is done in thoracic paracentesis.

It is advisable to have oxygen at hand for use if there is severe dyspnea, and artificial respiration should be applied if cessation of respiratory movements is imminent. There is one recorded instance in which the heart beat persisted for more than two hours while respiratory movements were maintained by hand, and it is possible that the use of a pulmotor may tide the patient over until the action of the toxin is exhausted.

The use of *botulinus antitoxin* has been most disappointing, because it is of value only when given early, before the toxin has become combined with the tissue cells. In laboratory tests with guinea pigs, the animals may be protected in all instances if the antitoxin is administered at the same time or very shortly after the toxin is injected, but the number of animals which survive rapidly decreases as the length of time between the administration of the toxin and antitoxin is increased, and there are very few instances in which the animals survive if the antitoxin is not given before the symptoms of intoxication develop.

In human outbreaks of botulism there have been no recorded instances in which there has been any definite benefit from the administration of antitoxin, because in all instances the antitoxin has been given after the onset of the symptoms. In 7 outbreaks in which the antitoxin which was administered was of the same type as the toxin which caused the poisoning, 33 persons were ill and 25 died. Seventeen of the patients died before the antitoxin was given and 8 succumbed after receiving the injections. One person recovered without having been given antitoxin and 8 recovered after it had been administered. The mortality in these outbreaks was 75.1 per cent. In all the instances in which persons recovered after receiving botulinus antitoxin, the more severely poisoned victims had died before the antitoxin was available, and none that were seriously ill when they received the antitoxin benefited by its use. Only those in which the onset of the intoxication was delayed, or in which the symptoms were of slight severity, recovered after its administration, and there is no reason to believe that the administration of antitoxin had anything to do with their recovery.

Nevertheless, specific antitoxin should be administered to all persons who have been exposed to botulinus intoxication as soon after the ingestion of the poison as is possible. Where chickens or other domestic fowl show signs of fowl botulism after eating discarded food from the kitchen, all persons who may have eaten any of the spoiled food should be given antitoxin even if they have not as yet shown signs of poisoning. There should be no delay, because it is in the cases where the toxin has not yet combined with the tissue cells that there is hope of benefit from the antitoxin.

Because botulinus intoxication in human beings is caused by the ingestion of a quantity of toxin at one time, and not by a constant supply which is being formed by development within the body, a single large injection of antitoxin, 20,000 units, is to be preferred to repeated small doses. It is advisable to use a polyvalent antitoxin or a mixture of both Antitoxins A and B rather than to wait until the type of the causative toxin can be determined. The patient should be tested for sensitization to horse serum, and desensitized if necessary, and the antitoxin should then be injected slowly, intravenously, preferably by gravitation, taking care that not more than 1 c.c. per minute is allowed to enter the vein for the first fifteen or twenty minutes. The danger of immediate ill effects or of subsequent serum sickness is no greater from botulinus antitoxin than from any of the other horse serum antitoxins.

Prophylaxis.—Clostridium botulinum is widely distributed in nature in the soil, and raw food materials, particularly vegetables and fruits, are liable to be contaminated with botulinus spores. Some of these spores are extremely resistant to heat and to other adverse conditions which are employed as preservative measures in processing foods, and some of the processes, particularly the home-canning processes, will not destroy the spores if they happen to be present in the raw material. It is always necessary, therefore, to consider it possible that preserved foods, which have not been processed at temperatures which are known to destroy the spores, may contain the botulinus toxin.

It is safe to say that there is always more or less marked evidence of spoilage when the food contains the botulinus toxin, but there is great variation in the extent to which the food is visibly spoiled. The typical cheeselike, butyric acid odor can usually be detected as soon as the container is opened, but occasionally it is masked and may escape notice unless the food is heated. In many instances there are unmistakable signs of spoilage, swelling of the ends of tin containers, loose caps on vacuum-sealed jars, signs of leakage, escape of gas under pressure when the container is opened, offensive odor, or disintegration of the more solid portions of the food; but in some instances the signs of spoilage may be very slight, and may escape notice unless the person who prepares the food is on the alert. A few instances are recorded where the persons who opened the containers, as well as those who ate the food served as salad with mayonnaise or vinegar, were agreed that there was no unusual taste or odor.

It is important, therefore, that persons who have to do with the serving of preserved foods should be constantly on the alert for any signs of variation from the normal, and that all preserved food which shows any sign of spoilage should be discarded.

The botulinus toxin is destroyed by boiling and there are no records of any outbreaks of poisoning in this country when the food was thoroughly cooked before it was consumed. In all recorded instances the food was either tasted "to determine whether it was spoiled" or was served as salad, dessert or relish without being sufficiently cooked after it was removed from the container. Cases are even recorded where persons who ate or tasted spoiled food before it was cooked developed botulism, whereas others who cooked the food before the meal escaped illness. It is, therefore, advisable to thoroughly boil all preserved foods before they are eaten unless it is known that the process by which they were preserved was sufficient to destroy all bacterial spores which might have been in the raw material.

The control of botulism does not, therefore, depend in any way upon curtailing the use of preserved foods, but necessitates the education of all who use them to know the possibility of poisoning from preserved foods and to recognize the signs of spoilage. If no spoiled preserved food is eaten, or if all preserved food is thoroughly boiled before it is eaten, the incidence of botulinus intoxication will be practically nil.

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CHAPTER XVIII

ANTHRAX

William H. Park

Prophylaxis.—Anthrax affects principally cattle, sheep, and horses, and from these is occasionally transmitted to man. The usual mode of infection in man is by contact with animals dead of anthrax, or by the handling of infected animal material, such as wool, hides, horsehair in shaving brushes, etc., which contain spores. The disease is found all over the world. In Russia large numbers of horses die annually from this disease, and the same is true of China. In Asia Minor the disease is prevalent among the Angora goats which supply much of the mohair of commerce. There is considerable anthrax among the countries along the Danube. It is also quite prevalent, though to a less degree, in England, Scandinavia, Spain, and Italy.

Anthrax infection is caused by a large spore-bearing bacillus. The spores are resistant to heat and disinfectants. Animals can be infected by inoculation, by feeding, and even by inhalation of the spores.

In animal infections the bacilli may be given off in the urine, feces, or sputum. The fields and pastures frequented by the diseased animals thus become infected with the spores and these are difficult to destroy. Rational prophylaxis, therefore, involves the proper disposition of the bodies of animals dead of anthrax, the exclusion of animals from fields known to be infected, suitable disinfection of the stalls, and finally protective inoculation against the disease.

In man the disease is almost always traceable to contact with anthrax infection in an animal. Out of 604 cases collected by Morebach, 178 occurred in butchers, 31 in persons engaged in spinning horsehair, 31 in shepherds and cowherds, 24 in hostlers, 17 in farmers and owners of cattle, 4 in veterinarians, 3 in quack doctors, and 2 in meat inspectors. In addition to this, cases have frequently been reported in workers in tanneries and brush factories, in furriers, etc. A number of cases have been reported as due to shaving brushes made of infected horsehair. The most frequent form of anthrax infection in man is that of the skin, producing what is called "malignant pustule." A rarer form is called "wool-sorters' disease," and represents a pulmonary infection due to inhalation of anthrax spores detached from the infected wool. Occasionally the infection is primary in the intestine.

Vaccine and Serum Treatment.—The development of vaccines for animals, although not applied practically in the immunization of man, is of interest.

In 1880 Toussaint reported that sheep could be immunized by injecting them with infected sheep blood heated to 55° C. for ten minutes. The heating, he believed, had destroyed all the anthrax bacilli. Pasteur, however, showed that this was not the case; the bacilli were not dead, but merely attenuated. In place of Toussaint's rather crude method of making such an attenuated vaccine, Pasteur devised the production of an attenuated culture by growing virulent anthrax cultures at high temperatures. In this way he was able to so reduce the virulence of the cultures that his Vaccine I was able to regularly kill white mice, but not always guinea pigs. Vaccine II regularly killed guinea pigs, but not always rabbits. In immunizing animals, 48-hour broth cultures of these attenuated vaccines are employed. Cattle receive 0.25 c.c. of Vaccine I, subcutaneously, and after twelve days a similar quantity of Vaccine II. Sheep receive about half these doses. Rabbits, guinea pigs, rats, and mice are extremely difficult to immunize. The immunity conferred on sheep and cattle by Pasteur's method of vaccination usually protects the animals against infection through the ordinary channels (stomach), as well as against injections of virulent cultures. The immunity lasts about one year. The vaccines must be very carefully standardized so as to be both effective and not dangerous.

It was found that the serum of animals artificially actively immunized against anthrax was able to confer a considerable degree of immunity on other animals. Sclavo produced a serum of which 2 c.c. protected rabbits against an anthrax infection which killed control animals within forty-eight hours. Moreover, he was able to save animals in which the serum was injected as long as twelve hours after infection. The best results were obtained when the rabbits were injected intravenously with the serum, while the virus was given subcutaneously.

Immunization against anthrax can also be effected by means of the combined method, that is, by injecting the animal simultaneously with specific antianthrax serum and anthrax culture. Ordinarily these injections are made on opposite sides of the body, the culture corresponding to Pasteur's Vaccine II. Cattle are injected with 5 c.c. serum and 0.5 c.c. of a suspension containing a loopful of culture in 50 c.c. sterile salt solution. In calves 0.3 to 0.5 c.c. of the culture suspension suffices. Horses require the same doses as cattle; sheep require 4 c.c. serum and 0.25 c.c. culture suspension. On the whole, the results of these combined immunizations have been very satisfactory.

In the production of the serum the successful results have been obtained by immunizing sheep and horses. So far as the technic of immunization is concerned, it does not differ from that employed in other cases of serum production. The animals are first made resistant against virulent anthrax, either by means of Pasteur's vaccines, or passively by the injection of specific antianthrax serum, or by the simultaneous injection of serum and culture. Once the animal is able to resist infection with a virulent culture, it is an easy matter to increase the degree of immunity by further injections. The immunization of horses and cattle can usually be pushed more energetically than that of sheep. The injections are ordinarily made at intervals of from ten to fourteen days, larger and larger doses being given. Subcutaneous injections have thus far given the best results. The animals are bled in from two to three weeks after the last injection. Horses differ greatly in the potency of the serum which they produce, so that several should be injected and the best chosen. The protective serum is now prepared by the United States Bureau of Animal Industry and also by some of the private biological plants. It is furnished like diphtheria antitoxin either as the whole serum or refined as a globulin preparation.

The serum appears to be useful in the cure of infections in which septicemia has not been established. In the treatment of anthrax infection in humans, Sclavo recommends from 30 to 40 c.c. distributed in several parts of the body; if there is no improvement the following day the injections are to be repeated. In severe cases he recommends intravenous injections. Recently the tendency has been to increase the doses in all moderate and severe cases to 50 and 100 c.c. of serum and to repeat the dose at 12-hour intervals until improvement is evident or the case is hopeless. In severe cases the first injection should always be given intravenously. Thus far the only extensive employment of this serum in humans has been in Italy and in Argentine. The reports on the whole are favorable. In Italy, according to Sclavo, the mortality has dropped from 24 per cent to 6 per cent. In connection with statistics, however, it must be remembered that the prognosis in malignant pustule is not unfavorable, and most of the human anthrax infections have been of this kind. The reports of the use of the serum in New York City, Boston and elsewhere are on the whole favorable when it has been given before septicemia has been established. I believe it is advisable to use the serum in all cases whether or not surgical measures are adopted. It would be of great value if careful reports were made of the results of the serum treatment. Some good results have been reported in cases in which the serum was given in small injections in the inflamed area in addition to that given intravenously.

The mode of action of antianthrax serum is not at all clear. Reasoning by exclusion, it has been held that its chief action is bactericidal.

Yet, so far as can be discovered with our present methods, the bactericidal power of anthrax serum is not different from that of normal serum. It does not appear likely that the effect is due to opsonins, for, when animals are injected with anthrax bacilli plus normal serum, and with anthrax bacilli plus antianthrax serum, no difference in the degree of phagocytosis can be made out. In fact, Sobernheim occasionally found that phagocytosis was more marked with the normal serum. In highly immunized animals infected subcutaneously with large quantities of anthrax cultures, it is often possible to find living, virulent anthrax bacilli at the site of injection for days afterward. Moreover, cases have been observed in which the blood of immunized animals swarmed with anthrax bacilli a week or more after infection.

With the exception of the use of serum, the treatment of anthrax is wholly surgical. Caustic potash has been recommended as a caustic, the tissues about the pustule to be protected by adhesive plaster.

CHAPTER XIX

GLANDERS

William H. Park

Occurrence.—Glanders occurs in almost all parts of the world, and is found especially in horses, donkeys, and mules.

Glanders is occasionally communicated to man by contact with infected animals, usually by inoculation on abraded surfaces of the skin. A number of investigators have shown that infection through the intact skin is most unlikely. Viborg (cited by Wladimiroff) showed that the same was true for mucous membranes, for he was able to place virulent glanders virus on the nasal mucous membrane of horses without infecting them. Infection occurred only when the virus was vigorously rubbed in. The relatively frequent occurrence of primary nasal glanders in horses is not surprising, when one considers the extreme liability of these parts to minute abrasions from the horse's food. The use of common drinking troughs or of common buckets is also believed to be an important factor in the spread of the disease in horses.

From what has already been said concerning the etiology of glanders infection, it is obvious that the pus from the ulcers and the secretion from the infected mucous membranes constitute the greatest source of the spread of the disease. Moreover, glanders bacilli may be present in the feces of infected animals, even though there are no intestinal lesions. This is comparable to the presence of tubercle bacilli in the feces of animals infected with pulmonary tuberculosis, and is due to the swallowing of the bacilli with coughed-up sputum or with infected nasal secretion.

Immunity.—So far as our present knowledge goes, a moderate immunity against glanders follows an attack of the disease.

Attempts have been made to produce artificial immunity against glanders in animals, and these are of interest, as the knowledge obtained can be applied to the treatment of subacute cases in man. Immunization has been attempted with an endotoxin prepared from glanders bacilli, and, while a certain degree of tolerance for this endotoxin could be produced, only a slight immunity against glanders infection was manifest. Since the introduction of mallein as a diagnostic agent we have learned that chronic glanders in horses does not infrequently end in spontaneous recovery. Working with cultures attenuated with glycerin and also with dead cultures, Levy appears recently to have successfully immunized animals against virulent infection, and Dedjulin reports favorable results in a number of horses. Silkman, in New York, has treated many horses with three immunizing injections of 2½ c.c. of a killed broth culture of the glanders bacilli, with apparently favorable results.

Treatment.—So far as specific treatment of glanders infection is concerned, a number of different procedures have been tried. Thus the serum of horses chronically ill with glanders has been injected into animals suffering from glanders, and favorable results are said to have been obtained. The number of cases thus treated, however, is too small to permit definite conclusions, and confirmatory observations are lacking. In view of the fact that cattle are relatively immune to glanders infection, Nicolle has experimented with defibrinated ox blood as an immunizing agent, and believes his results warrant further trial of the method. In the hands of other investigators the results have been unsatisfactory.

Wright, Bristow, and White, and recently Cramp and Zieler, report recovery from glanders in man following the administration of bacterial vaccines. We know of two subacute cases which recovered under this treatment. In view of the very grave prognosis in these infections when treated by the ordinary methods, treatment with bacterial vaccines should be tried in all except possibly the very acute cases. The doses employed have varied somewhat, and will depend on the degree of reaction produced. It is well to begin with injections of 60,000,000, increasing, by additions of 20,000,000, up to 200,000,000, or to a point where a definite reaction is produced. The reaction from the injections is similar to that produced by mallein. If a larger dose than the one advised is given, a too severe reaction may occur due to sensitization. The injections are usually given every four or five days, but may in smaller doses be given every two days.

There is no non-specific treatment for glanders which differs from that suitable for any other acute infectious disease. The discharges from the nose and mouth and from any lacerated surfaces should be carefully looked after and disinfected.

CHAPTER XX

TETANUS

William H. Park

The treatment of tetanus has two distinct purposes: (1) the neutralization of the tetanus toxins and the freeing of the wound from infection; and (2) the sustaining of the patient and the alleviation of the symptoms until the effects of the specific poison subside, as shown in the relaxation of the muscular contractions.

Bacterial Poisons.—The characteristic symptoms of tetanus are caused almost wholly by a very powerful poison produced by the tetanus bacilli. This is called tetanospasmin. This poison is given off by the bacillus and is of such toxic powers that 0.000,005 gm. will kill a mouse. There is a second poison elaborated by the bacilli called tetanolysin, which has the power to cause lysis of the red blood-cells. This is less in amount and less toxic. Some consider it as a factor in the anemia occurring, but it probably has little deleterious effect. The endotoxins in the protoplasm of the tetanus bacilli are of no importance, since the tetanus bacilli develop only in small numbers, and long before the endotoxins could accumulate in appreciable amounts the more powerful tetanospasmin would cause death. The tetanus bacilli remain almost wholly at the site of the wound, a few only are carried to the blood and scattered throughout the body. These isolated bacilli apparently do not proliferate.

Source of Infecting Tetanus Bacilli.—It is a peculiar fact that these bacilli live and multiply in the intestinal contents of horses, cattle, dogs, and even men without causing injury. Unless the mucous membrane is wounded neither the tetanus bacilli nor their toxins are absorbed. The feces scatter the bacilli and their very resistant spores over the soil. These, consumed with the grass or inhaled with the dust and caught on the nasopharyngeal mucous membrane enter the intestines of other animals and men.

As a rule, the warmer the climate the greater the proportion of animals and men with tetanus-infected feces. Certain localities are known to be especially liable to tetanus infection, such as Eastern New York and Connecticut. The spores are very resistant, living almost indefinitely when protected from sunlight and moisture.

Means by Which Wound Infection Occurs.—The tetanus bacilli and spores unaccompanied by other bacteria do not develop readily if located in healthy tissues. If, however, the tissues are injured, or they are accompanied by other bacteria or by foreign materials, the tetanus spores then develop and multiply and poisoning occurs. This is especially liable to take place in a ragged penetrating wound where the tissues adjacent to the infection are somewhat lacerated. The presence of a foreign body such as catgut, the waste from a blank cartridge, shreds of clothing, or simply dirt add to the danger. The additions to the foreign material of a few pathogenic or putrefactive bacteria add still further to the probability of infection. If the wound is quickly and thoroughly cleaned infection is usually avoided, but if it is neglected, or if because of its nature it cannot be cleaned, tetanus may develop.

Preventive Treatment.—The surgical treatment has for its object the removal of all foreign material including bacteria from the wound, in so far as that is possible.

The surrounding parts should be thoroughly cleaned with soap and water, and the wounded tissues cleansed with sterile salt solution. All dirt, bits of clothing, and any foreign material should be carefully removed. Finally a thorough cleansing with some suitable disinfectant solution should be carried out. If the danger of tetanus or other bacterial infection is great, pack the wound lightly with antiseptic gauze. Inject in all suspected cases from 1,000 to 2,000 units of tetanus antitoxin subcutaneously. The smaller dose is sufficient for young children and adults having but slight wounds. The antitoxin is eliminated at the end of two weeks. It is therefore essential to repeat the injection at the end of ten days in all cases where the wound is extensive or sloughing of tissues occurs. In these cases tetanus toxin may continue to be elaborated and absorbed. It is wise to give a third injection at the end of another ten days, if the wound has not healed. By giving these repeated injections to the wounded in the late war the occurrence of tetanus was almost completely prevented.

Diagnosis.—This is generally made through the symptoms, and there is usually no need of a bacteriological examination before treatment is instituted.

The first suspicious symptoms should be the signal for immediate injection of antitoxin. If the case is one of tetanus the symptoms will develop in spite of this sufficiently to make the diagnosis certain. Bacteriological tests may be valuable in doubtful cases in confirming the diagnosis or in disproving it.

An infant, for instance, was reported as having developed fatal tetanus after vaccination. The skin and subcutaneous tissues were excised at the point of vaccination and placed in broth under anaërobic conditions. The absence of the development of tetanus bacilli, together with the discovery at autopsy of an intense gastritis, eliminated the diagnosis of tetanus.

Paths by Which Tetanus Toxin Reaches Central Nervous System.—It is a matter of great practical importance to discover the course of the toxin from the wound to the cells of the brain and spinal cord, because our methods of injecting the antitoxin will be greatly influenced by the location of the toxin in the tissues at the time symptoms develop. Much experimental work has been done in investigating this subject. All agree that the toxin is taken up to some extent by the nerves. Some believe that this is wholly through the end nerve plates, and that the toxin passes along the nerve fibers until it reaches the spinal cord. Others think that the toxin passes up the lymph vessels of the nerves. There can be no doubt that a considerable amount of the toxin passes up the nerve trunk, supplying the region of the infection, but probably much the larger part is taken up by the tissue lymph spaces and carried through the lymph channels to the blood current, and there distributed through the body to pass out from the blood capillaries and be, if not already neutralized, taken up by the nerve endings everywhere throughout the whole body. The most important investigations upon this point may be summed up briefly as follows:

Gamprecht and Stintzing concluded from their experiments that the toxin from the wound passed to the central nervous system, partly directly by the perineural and endoneural lymph spaces of the nerves of the infected region, which directly connected with the subdural spaces, and partly through other nerves obtaining it indirectly from the blood. The local tetanus they considered as due to the contact of the poison with the motor end plates.

The experiments of Meyer and Ransom and of Marie and Morax proved to their satisfaction that the poison is transported to the central nervous system by the way of the motor nerves—and by no other channel. These authors thought that they had shown that the essential element for the absorption and transportation of the toxin is not the lymph channels, but the axis-cylinder, the intramuscular endings of which the toxin penetrates. Marie and Morax were able to demonstrate the poison in the nerve corresponding to the area of infection one and one-half hours after treatment. Absorption, however, and conduction are dependent to a large extent on the nerves being intact. A nerve cut across takes very much longer to take up the poison (about twenty-four hours), and a degenerated nerve takes up no poison whatever. In other words, section of the nerve prevents the absorption of the poison by way of the nerve channels. Similarly section of the spinal cord prevents the poison from ascending to the brain. The poison which passed through the general lymph channels to the blood was partly returned to the tissue fluids throughout the body and taken up by the nerve endings and thus produced general tetanus. According to Meyer and Ransom, the reason sensory nerves do not play any rôle in the conduction of the poison is because the spinal ganglion places a bar to the advance of the poison.

Ascending centripetally along the motor paths, it reaches the motor spinal ganglia on the side of inoculation and affects the ganglia of the opposite side, making them hypersensitive. The visible result is the highly increased muscle tonus, that is, rigidity. If the supply continues, the toxin next affects the nearest sensory apparatus; there is an increase in the reflexes, but only when the affected portion is irritated. In the further course of the poisoning the toxin as it ascends continues to affect more and more motor centers, and also the neighboring sensory apparatus leading to spasm of all the striated muscles and general tetanus.

Field has shown that not only tetanus toxin, but diphtheria toxin and inert colloids, can be demonstrated in the sciatic nerves after they have been injected subcutaneously or intramuscularly, and after varying periods may be found in the spinal cord. He believes that the toxin passing up nerve trunks is absorbed mostly by way of the lymphatics of the nerves.

Cernovodeanu and Henni confirm this contention. They ligated all the muscles and blood-vessels in a guinea pig's leg, leaving intact only the sciatic nerve, skin, and bone, and then injected a large amount of tetanus toxin below the point of ligation. The animals never developed tetanus. There was only a very slight flow of lymph into the ligated area, and therefore only a slight flow up the nerve.

The larger part of the toxin is carried by the lymph of the infected region to the blood, and if not neutralized is transmitted to the tissue fluids. The path of absorption to the central nervous system is then by way of the motor nerve tracts of the whole body.

Union of Toxin with Gray Matter of Brain and Spinal Cord.—This union is a loose one, and the toxin can be partially freed from its union by the action of proteolytic ferments. A number of different elements of the cell substance seem to have this power of binding the toxin. Heating to 65° C. for ten minutes destroys the capacity to fix toxin. These brain substances which unite with toxin are certainly not of the nature of antitoxin, and the brain cells, if they produce antitoxin at all, certainly share the power with other cells. Marie notes that adrenalin neutralizes tetanus toxin, and that lecithin compounds are concerned in the mechanism of the action of tetanus toxin on nerve cells.

Period between Absorption of Toxin and Development of Symptoms.—There is, however, apparently an interval of time in which the toxin is in contact with the cells' surface, or is free in the cells' fluid, before true union takes place. According to experiments by Kraus, part of this toxin will pass out of the cells if they are surrounded by an antitoxic fluid, just as salts pass through a membrane into salt-free fluids. After the absorption of the poison there is a lapse of time before any effects are noticed. With the injection of an enormous amount, such as 90,000 fatal doses, there is about nine hours; with 30,000, ten; with 3,000, twelve; with 10 fatal doses, fifteen to eighteen; with 2 fatal doses, fifteen to twenty-four. Less than a fatal dose will produce local symptoms in forty-eight to seventy hours. When living cultures are injected longer periods elapse, for then the toxins require time for production.

Muscles Involved.—The parts first to be affected with tetanus are, in about one-third of the cases in man, and usually in animals, the muscles lying in the vicinity of the inoculation—for instance, the hind foot of a mouse inoculated on that leg is first affected, then the tail, the other foot, the back and chest muscles on both sides, and the forelegs, until finally there is a general tetanus of the entire body. In mild cases, or when a dose too small to be fatal has been received, the tetanic spasm may remain confined to the muscles adjacent to the point of inoculation or infection. The symptoms following a fatal dose of toxin vary greatly with the method of injection. Intraperitoneal injection is followed by symptoms which can hardly be distinguished from those due to many other poisons. In man the first symptoms are usually those of a contraction of the muscles of the lower jaw, and then those of the neck.

Presence of Tetanus Toxin in Blood.—The blood during the first four days of the disease, if no antitoxin is given, usually contains toxin. After that time antitoxin usually develops and soon makes the blood antitoxic. In St. Louis some years ago the serum of a horse dying of tetanus was given by accident in doses of 5 to 10 c.c. to a number of children, with the development in some of fatal tetanus. In this connection Bolton and Fisch showed by a series of experiments that considerable toxin might accumulate in the blood before symptoms became marked. In the cases of human tetanus examined, the amount of toxin present in the blood has not been large.

Endotoxins.—These are so much less poisonous than the tetanospasmin that they do not have any appreciable influence on the development of disease.

TREATMENT OF TETANUS

Protective Action of Tetanus Antitoxin.—Behring and Kitasato were the first to show the protective and curative effects of the blood serum of immunized animals. It was found that animals could be protected from tetanus infection by the previous or simultaneous injection of tetanus antitoxin, provided that such antitoxic serum was obtained from a thoroughly immunized animal. This neutralization was due to a chemical union between the two substances. From this it was assumed that the same result could be produced in natural tetanus in man. Unfortunately, however, the conditions in the natural disease are very much less favorable, inasmuch as treatment is usually commenced, not shortly after the infection has taken place, but hours after the tetanic symptoms have appeared, when the poison has already attacked the cells of the central nervous system and to some degree permanently combined with them.

Production of Tetanus Antitoxin for Therapeutic Purposes.—The tetanus antitoxin is developed in the same manner as the diphtheria antitoxin—by inoculating the tetanus toxin in increasing doses into horses. The horses receive 5 c.c. as the initial dose of toxin, of which 1 c.c. kills 250,000 gm. of guinea pig, and along with this twice the amount of antitoxin required to neutralize it. In five days this dose is doubled. This overneutralized toxin stimulates the production of antitoxin. Recently we have preferred to inject the horses subcutaneously with 5,000 units of tetanus antitoxin, and then, after a lapse of twenty-four hours, give, at short intervals, increasing doses of straight toxin. After four or five months of this treatment the blood of the horse contains the antitoxin in sufficient amount for therapeutic use. Horses usually have about 100 units, but some have produced as high as 600 units per cubic centimeter. The antitoxic serum is refined by eliminating all substances except the pseudoglobulins. As in the case of diphtheria antitoxin the tetanus antitoxin is bound with the pseudoglobulins of the horse serum.

Antitoxic Unit and Technic of Testing Antitoxin Serum.—Tetanus antitoxin is tested exactly in the same manner as diphtheria antitoxin, except that the size of the unit is different. In 1907 the producers of serum in the United States agreed to a unit of antitoxin which is approximately ten times the size of the unit of diphtheria antitoxin. A unit is defined as the amount of antitoxin required to just neutralize 1,000 minimal fatal doses of tetanus toxin for a 350-gm. guinea pig. The United States Government has adopted this unit, and supplies the different producers for testing purposes with standardized toxin.

Antitoxic Units Adopted by Foreign Governments.—The European countries have recently adopted a unit which equals one half of the American unit. Other countries will finally adopt either the American or the European unit.

Persistence of Antitoxin in Blood.—Ransom has clearly shown that the tetanus antitoxin, whether directly injected or whether produced in the body, is eliminated equally slowly from the blood of an animal, provided that the serum is from an animal of the same species. If from a different species it is much more quickly eliminated and has practically disappeared in from ten to twenty-one days.

Absorption of Toxin and Antitoxin from Tissues.—The same investigator made very extensive and interesting observations on the absorption of the tetanus poison by the lymph vessels and its accumulation in the blood; he also made similar observations on antitoxin. He inserted in the thoracic duct of a dog a cannula and then injected in the subcutaneous tissues of the left inguinal region a large number of fatal doses of tetanus toxin. In another dog he performed the same experiment, except that he substituted antitoxin for toxin. He took samples of the lymph every few minutes after giving the injections, and measured the amount of toxin or antitoxin, as the case might be. He also made an experiment in which, some hours after the toxin had been administered, he later administered the antitoxin in another part of the body, and noted the time at which the toxic lymph became neutralized and then antitoxic. The following two tables show the result of the injection of the toxin and of the antitoxin:

Table I—Absorption of Toxin in Dogs as Shown in Lymph and Blood

	Lymph	
Time	Duration	Fatal Toxic Doses for a Mouse in 1 c.c.
Minutes	15 to 30	0
Hours	1 to 1½	10
Hours	2 to 2½	100
Hours	3 to 3½	200
Hours	4 to 4½	500
Hours	5 to 5½	1,280
	Blood	
Minutes	15	0
Hour	1	5
Hours	4	25
Hours	6	35

Table II—Absorption of Antitoxin

	Lymph	
Time	Duration	Number of Mouse Units of Antitoxin
Minutes	0 to 15	trace
Minutes	15 to 30	50
Hours	1 to 1½	6,000
Hours	2 to 2½	25,000
Hours	3 to 3½	55,000
Hours	4 to 4½	100,000
	Blood	
Hour	1	100
Hours	4	200
Hours	6	300

It is noticed that in the above tables the lymph remained up to thirty minutes free of toxin. It then began to appear in increasing amounts up to the end of the experiment at five hours. The blood remained free from toxicity as long as the lymph and then to a lesser degree, so that there is no question but that the blood-vessels themselves did not take up any appreciable tetanus toxin except as it was delivered to the blood-stream by the lymph. In the second experiment in which the antitoxin was injected it is noticed that even at fifteen minutes a trace of antitoxin appeared in the lymph. This rapidly increased until the end of the experiment at four and one-half hours. Here, again, the blood-stream accumulated antitoxin only as it was poured in by the lymph. In a third experiment an intravenous injection of antitoxin was given. In a very few minutes the lymph showed distinct amounts of tetanus antitoxin. This rapidly increased in amount until in a short time the lymph contained one-third as much as the blood. This relationship between the blood and the lymph continued for several days, the antitoxin in both gradually lessening. The same experiment was tried with the tetanus toxin, and within fifteen minutes the lymph was strongly toxic. This relationship continued, the amount in both blood and lymph gradually diminishing.

A final experiment was then made by injecting a dog with the tetanus toxin. After twenty-four hours the thoracic duct was tapped and the lymph tested. Each cubic centimeter was found to contain 45 fatal doses for a gram of mouse. A large injection of antitoxin for each gram of dog was then injected intravenously, and lymph specimens taken from time to time. The result of the test showed that during the first fifteen minutes the lymph continued with undiminishing toxicity. During the next fifteen minutes toxicity dropped to one-half the amount, and in the next fifteen minutes it became neutral. At the end of an hour the lymph was antitoxic. The results showed that an intravenous injection of antitoxin immediately neutralizes the blood, and in about thirty minutes, or shortly after, makes the lymph antitoxic. The spinal fluid is much slower than the lymph in showing antitoxin, and it never accumulates to any great extent, the final ratio being 1 to 100.

In 1898 Roux and Borrel suggested the treatment of tetanus through the direct injection of antitoxin into the central nervous system by cerebral or lumbar injection. They considered that they got better results than from subcutaneous injections. Ransom investigated this matter and found that a subdural injection is practically the same as injecting anywhere in the subarachnoid space. He found that after subarachnoid injection, either in the region of the brain or the spinal cord, the antitoxin rapidly passes by way of the lymph into the blood, so that all but a trace has disappeared within twenty-four hours. He found that the tissues of the central nervous system contained no antitoxin, and that hardly a trace remained in the spinal fluid. He then injected tetanus toxin into the subarachnoid space, both by injecting through the brain tissue and by lumbar puncture. He found that a portion of the toxin appeared in the blood, while a large portion remained attached to the central nervous system, and that after such an injection the substance of the central nervous system lost its normal power to neutralize toxin and had become toxic. He proved that this was not because of any remaining toxin in the cerebrospinal fluid. He also found that the spinal cord matter always contained more toxin than that of the brain. He found that when moderate amounts were injected the blood contained no toxin, while the brain and spinal substance were toxic.

Absorption of Tetanus Antitoxin from Subcutaneous Tissue of Man.—In order to test the absorption of tetanus antitoxin in man, and to learn the length of time it remained in the blood, I injected a healthy adult subcutaneously with 10,000 units of antitoxin. The results, as tested in bleedings taken at intervals during six days, were as follows:

At 18 hours each c.c. contained	0.5 unit
At 24 hours each c.c. contained	0.8 unit
At 48 hours each c.c. contained	1.0 unit
At 72 hours each c.c. contained	1.0 unit
At 144 hours each c.c. contained	0.8 unit
At 2 weeks each c.c. contained	0.2 unit

The charts of cases of diphtheria injected either subcutaneously or intravenously are of interest, as they undoubtedly parallel cases of tetanus injected with tetanus antitoxin. The charts show that it is impossible to make the blood strongly antitoxic in a few hours by subcutaneous or intramuscular injections.

With Dr. Matthias Nicoll, Jr., I some time ago compared subcutaneous, intravenous, intraneural, and intraspinal injections. The results with intraspinal injections were considerably better than with intravenous and those with intravenous injections did much better than those receiving subcutaneous injections. The intraneural injections had no appreciable effect. The units required by the intraspinal method were less than by the other methods. Repeated large injections did not give any better results than a single sufficiently large injection. The above table gives the striking results obtained in one representative experiment. March 24, 15 guinea pigs were injected in the hind leg with 2 minimal fatal doses of toxin. March 25, 13 of these were given antitoxin as shown in the table.

Results in Man.—In actual cases in which the treatment was given within six hours of the development of symptoms the results observed by us have been surprisingly good. The recoveries in the cases treated by intraspinal injections have been over 70 per cent. In some cases no beneficial results appeared. We have seen numerous cases of generalized tetanus that, after a moderate intraspinal and large intravenous injection, have markedly improved, and finally recovered, and these cases have cer-

Table III—Comparison of Results of Treating Tetanus in Guinea Pigs by Intracardial, Intraneural and Intraspinal Injections of Antitoxin

Number	Weight (Grams)	Condition of Leg	Method	Amount in Units	Result
116	290	fairly stiff	control	...	died 3 days
42	310	fairly stiff	control	...	died 3 days
296	250	slightly stiff	Heart	100	died 8 days
227	275	fairly stiff	Heart	100	died 4 days
399	300	fairly stiff	Heart	100	died 5 days
316	255	slightly stiff	Nerve	200	died 4 days
287	255	fairly stiff	Nerve	200	died 3 days
879	265	fairly stiff	Subc.	500	died 3 days
198	305	slightly stiff	Subc.	500	died 5 days
48	320	fairly stiff	Subc.	500	died 3 days
289	280	fairly stiff	Nerve	200	died 3 days
306	285	slightly stiff	Nerve	200	died 3 days
59	255	stiff	Spinal Canal	10	Disch. normal 4/23
304	275	fairly stiff	Spinal Canal	10	Disch. well, 4/23 drags leg.
321	320	fairly stiff	Spinal Canal	10	Disch. well, 4/23 drags leg.

tainly done much better than apparently similar ones receiving palliative treatment alone. Lambert, who, some years ago, made an exhaustive study of tetanus, states that in a total of 114 cases of this disease treated with antitoxin by the older method, according to published and unpublished reports, there was a mortality of 40.35 per cent. Of these 47 were acute cases—that is, cases with an incubation period of eight days or less, and with rapid onset, or cases with a longer period of incubation, but intensely rapid onset of symptoms; of these the mortality was 74.46 per cent. Of the chronic type—those with an incubation period of nine days or more, or those with shorter incubation with slow onset—there were 61 cases with a mortality of 16.39 per cent. With a still larger number of cases the results indicate that with tetanus antitoxin about 20 per cent better results are obtained than without. I have always believed that when antitoxin is given more promptly, in sufficient first doses and by the best methods, the results will be much better than those quoted by Lambert. The results tabulated some time ago by Ernest E. Irons bear out this opinion. All but 20 of the 245 cases were treated in large hospitals.

The cases tabulated by Dr. Irons apparently demonstrated that cases treated with antitoxin did better than those not receiving it, and those having large doses better than those receiving small doses. The examination of the last table would apparently show that those receiving the injections on the second and third days did better than those receiving them on the first. This is due undoubtedly to the fact that the most acute cases were those which came first to the attention of the surgeon or the physician and, therefore, received antitoxin on the first day. Those in which the tetanus developed slowly delayed seeking treatment and, therefore, one or two days elapsed. Such cases, if they had been acute, would have been dead before the time they received their treatment. Even those receiving treatment in the first twenty-four hours should, if that was in the later hours of the day, be considered as receiving injections late. There is no question that every hour counts and that those receiving intraspinal or intravenous injections within the first few hours of definite symptoms show a much greater percentage of recovery than those given in the table by Dr. Irons. During the past few years intraspinal injections have been given in nearly every case occurring in New York City. Dr. Nicoll and I collected the first 20 cases. The results showed 80 per cent of recoveries. Later results in cases reduced the recoveries to about 60 per cent.

TABLE IV—COMPARISON OF CASES TREATED WITH SERUM AND WITHOUT SERUM

Cases Treated with Serum

Incubation (Days)	Total Cases	Died	Recovered	Mortality (Per Cent)
5	38	27	11	....
6	18	15	3	....
7	21	16	5	....
8	17	14	3	....
9	24	17	7	....
10	13	7	6	....
	131	96	35	73.28
11 to 15	47	22	25	....
16 and over	22	6	16	....
	69	28	41	40.57
Total all cases incubation known	200	124	76	62.
Incubation unknown	25	15	10	60.
Total all cases receiving serum	225	139	86	61.77

Cases without Serum

Incubation (Days)	Total Cases	Died	Recovered	Mortality (Per Cent)
10 or less	11	10	1	....
Over 10	4	2	2	....
Unknown	5	5	0	....
	20	17	3	85.

TABLE V—RESULTS WITH RESPECT TO (1) TIME WHEN SERUM WAS GIVEN, (2) SIZE * OF DOSE IN FIRST 24 HOURS

A. Cases receiving first serum within 24 hours of appearance of first symptoms

Incubation (Days)	Large Doses		Small Doses		Mortality	
	Died	Recovered	Died	Recovered	Large Doses	Small Doses
10 or less	41	13	21	3	75.9	87.5
Over 10	11	15	6	3	42.3	66.6
Totals	52	28	27	6	65.0	81.8

B. Cases receiving first serum in second 24 hours after appearance of first symptoms

Incubation (Days)	Large Doses		Small Doses		Mortality	
	Died	Recovered	Died	Recovered	Large Doses	Small Doses
10 or less	11	9	6	..	..	..
Over 10	2	8	1	..	..	..
Totals	13	17	7	..	..	..

C. Cases receiving first serum over 48 hours after first symptoms

Incubation (Days)	Large Doses		Small Doses		Mortality	
	Died	Recovered	Died	Recovered	Large Doses	Small Doses
10 or less	10	6	7	4	..	..
Over 10	7	10	1	5	..	..
Totals	17	16	8	9	..	..

D. Totals for the three periods

Incubation (Days)	Large Doses		Small Doses		Mortality	
	Died	Recovered	Died	Recovered	Large Doses	Small Doses
10 or less	62	28	34	7	68.8	82.9
Over 10	20	33	8	8	37.7	50.0
Grand Totals..	82	61	42	15	57.3	73.7

* A small dose 3,000 units or less subcutaneous. A large dose over 3,000 units subcutaneous or 3,000 or less intraspinal or intravenous.

In judging the effect of antitoxin given intraspinally in this series of cases, it must be remembered that the patients were not selected, but that every case of tetanus reported was given the benefit of the treatment regardless of the clinical condition. The series, therefore, may be said to be fairly representative of the type of the disease occurring in and about the city of New York. A few of these patients would undoubtedly have recovered if the intraspinal injection of antitoxin had not been given or, indeed, without any treatment other than symptomatic. The results obtained, however, in the saving of life are so much more favorable than those in previous years, when large doses of antitoxin were recommended to be given by the intravenous and subcutaneous methods, that there can be no reasonable doubt that the low death-rate, 20 per cent, here obtained was partly due to intraspinal dosage and partly to the very early use of antitoxin.

Actual Antitoxic Treatment of a Case of Tetanus

A case of tetanus should be injected at the first possible moment after the development of suspicious symptoms.

The best results are obtained through the combined intraspinal and intravenous injections, the next through intraspinal and intramuscular injections. Subcutaneous injections are much less efficacious because of the slow absorption. Injection into the ventricles of the brain is more dangerous than by the intraspinal way, and presents no advantages. An injection into the trunk of the nerve supplying the infected part is theoretically of value, but when an intraspinal, or even an intravenous, injection has been made it is of no practical value. Injection of antitoxin into the tissue of the cord itself is unnecessary, and does not add to the protection given by the intraspinal way. The intraspinal injection in an infant or child should be from 2,000 to 5,000 units, according to its size; in an adult 10,000 to 15,000 units.

The amount of fluid should be as large as can be injected, without causing pressure symptoms, so as to spread as thoroughly as possible throughout the subdural space. If the serum is thick it should be diluted with normal salt solution or sterile water.

The patient should lie on the right side with the knees drawn up and the left shoulder depressed. The skin of the patient's back, the hands of the operator, and the syringe should be sterile. The needle should be 4 cm. in length, with a diameter of 1 mm. for children, longer for adults.

The puncture is generally made between the third and fourth lumbar vertebræ. The thumb of the left hand is pressed between the spinous processes, and the point of the needle is inserted in the median line, or a little to the right of it, on a level with the thumb nail, and directed slightly upward and inward toward the median line. At a depth of 3 or 4 cm. in children and 7 or 8 cm. in adults the needle enters the subarachnoid space, and on withdrawing the obturator the fluid flows out in drops or in a stream. After the flow of fluid has stopped a container holding the thinned antitoxic solution is connected by a short rubber tube to the needle, and the requisite amount of antitoxic fluid allowed to run in by gravity. If for any reason sufficient fluid will not enter the canal gentle pressure is used. Use 5 c.c. to 20 c.c., according to age.

The amount of antitoxin advised to be injected is many hundred times as much as is necessary to neutralize the toxin, if only it can reach it. The antitoxic fluid should be warmed to blood heat.

Besides the intraspinal injection, an intravenous injection should be given so as immediately to neutralize the toxin in the blood, and soon afterward that in the lymph. The size of the individual, rather than the severity of the case, determines the amount to be given, for, in tetanus, every case is very grave. A good rule is to give 2,000 units for every 10 pounds. A child of 40 pounds would receive 8,000 units. The serum should be warmed to body heat and given slowly. All precautions to avoid infection should be used, so far as the general body is concerned.

These two injections suffice for the antitoxin treatment of the case except for further intraspinal injections, as the blood will remain strongly antitoxic for five days. This is plainly seen in the table on the Absorption of Antitoxin (see page 451), showing the antitoxin in the blood after the lapse of a week. The intraspinal injections had better be repeated after twelve, twenty-four and forty-eight hours. The antitoxin rapidly passes from the spinal fluid to the blood and it is possible that some toxin may enter the cord from the nerve trunks. The repeated injections certainly seem to do good. The important thing is to give enough at the first possible moment. On the fifth, seventh and tenth days a subcutaneous injection of 10,000 units is advisable in order to keep up the antitoxic strength of the blood, so that if toxin may still be developing it will be harmless.

When one is unable to give the antitoxin intraspinally or intravenously, then it should be given intramuscularly without delay, and if possible a later intraspinal and intravenous injection can be given. When antitoxin is given subcutaneously or intramuscularly, the amount should be twice as much as when given intravenously. When the amount of antitoxin available is less than the desired amount it should be given immediately, and then later, when a further supply is obtained, the remainder should be given. The British Tetanus Committee recommended in 1918 the following dosage:

Dosage Recommended by British Tetanus Committee

Day	Subcutaneous	Intramuscular	Intraspinal
First	....	8,000	16,000
Second	....	8,000	16,000
Third	....	4,000	.....
Fourth	....	4,000	.....
Fifth	2000 to 4000	....	.....
Sixth	....	....	.....
Seventh	2000 to 4000	....	.....
Eighth	....	....	.....
Ninth	2000 to 4000	....	.....

DRUG TREATMENT[1]

Anodynes and spinal sedatives are usually employed, and with an advantageous result in mild cases. They have no power to cure, but there is no doubt that they relieve pain and diminish spasm, and so conserve the strength and possibly prevent suffocation. To produce these effects in mild cases, or any effects at all in the acute and severe cases, large or very large doses are necessary; and it may well be that some of the remedies in these amounts are not devoid of danger.

Bromid of potassium, the safest and one of the most effective, may be given in much larger quantity than writers usually advise; indeed, an abundant experience shows that the human body will tolerate 2 drams at a dose without harm. In tetanus it is desirable that such doses be administered by the stomach or nasal tube, or by the rectum, and be frequently repeated. The effect is enhanced by adding chloral, of which 15 gr. (1.0 gm.), 30 gr. (2.0 gm.), and even 60 gr. (4.0 gm.) may be given every six to twelve hours; its dangers perhaps being exaggerated. Yet, undoubtedly, it is a judicious caution to watch its effects, and to govern the dosage by the effect produced.

The spasms are also powerfully influenced by the preparations of Calabar bean, notably the fluid extract and the sulphate of eserin. Both must be pushed, eserin being given subcutaneously in doses of 1/6 gr. (0.01 gm.) every three hours until its physiological effect is shown in fibrillary twitching of the muscles and diarrhea. This drug may properly be mentioned here, not that it is, as a remedy, any great favorite at the present day. Other remedies, little used now, but esteemed by the older physicians, are conium, gelsemium, nicotin, aconitin, and amyl nitrite. The last is most useful, but all require practice and a special knowledge to be employed with success.

If the current opinion be true, chloretone is a remedy of peculiar excellence. It is given in large doses at a single time, 40 gr. (2.6 gm.) in olive oil by the rectum, and 120 gr. (8.0 gm.) in twenty-four hours. Unfortunately its action is obscure, and Begbie reports a case in which it may have had some influence in causing death.

Some cases are greatly benefited by chloroform inhalations during severe spasms, and may even absolutely require it. No remedy for tetanus, however, has been more indiscriminately used. On this point the differences between doctors are profound; but there is a growing conviction that the prolonged administration of chloroform is harmful.

Similarly morphin and atropin are valued highly; but these are not cures, and are both used and abused. They have special uses—to relax the muscles and produce sleep; and atropin has a particular merit—that of drying the mucus in the mouth and throat. Morphin, when used, should be combined with atropin, but atropin may very well be used alone. Few remedies are more easy to interpret; the signs of toxic action in atropin are particularly legible. Large doses of both drugs should be given, and Leyden rightly advises .02 gm. morphin (1/3 gr). During the twenty-four hours 0.1 to 0.15 gm. can be given. Atropin should be injected into the rigid muscles, the maximum dose being 1/25 gr. (0.0025 gm.).

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[1] I wish to thank Dr. Bartholow for his assistance in preparing this section.

Of late years two forms of "symptomatic" treatment have been before the progressive physician: (1) with phenol, and (2) with magnesium sulphate.

1. Bacelli's method is the subcutaneous injection of large doses of phenol. The results claimed are most striking. He uses a 2 to 3 per cent solution in water, and begins by administering 0.3 to 0.5 gm. carbolic acid daily, divided in several injections. He then increases the quantity to 1½ gm. daily. Maragliano recommends a 5 per cent solution in oil. Bacelli claims that it lessens the nerve excitability of the spinal cord, lowers the temperature, and has antitoxic properties. The method has been approved by many, while others have had little success with it. In animal experiments it appears to have little or no effect—certainly much less than antitoxin. The statistics given show a remarkably low mortality—of less than 10 per cent. These figures are undoubtedly too good.

In my own experience the good results have not been evident and I am sure that if given it should be in addition to, and not in the place of, antitoxin. The urine must be carefully watched.

2. Magnesium sulphate is administered in two ways: subcutaneously and into the spinal canal. It is not easy to discriminate between what is more and what is less beneficial in them. The subcutaneous method is doubtless the safest and easiest; it has also proved useful. A slight overdose has caused dangerous and profound collapse, as in Miller's case. Deaths are reported by Page, Phillips, Debré, and Tanton, and, though cures occur, a close examination of many shows that antitoxin, bromids, chloral, and atropin were also used. The chief danger is from respiratory failure—a danger only avoided by very careful dosing. Meltzer's original dose was 1 c.c. of a 25 per cent sterile solution to every 25 pounds of body weight. This dose by some is slightly reduced.

The technic of the injection may be thus described: A lumbar puncture is made between the third and fourth vertebræ. The patient should be placed on his left side with the head slightly raised, to prevent the solution from flowing into the medulla and paralyzing the respiratory center, an accident, nevertheless, which has more than once taken place. Chloroform may be required, but should be avoided where that is possible. If the puncture is successful, a small amount of the spinal fluid is allowed to flow through the needle, and it is then affixed to the syringe containing the solution of magnesium sulphate. The method, which should be practiced by the expert alone, is dubious to a degree. For, as Taylor writes, "the treatment is symptomatic, can only be partial, and is not free from danger."

In this enumeration of remedies the properties of pilocarpin should be mentioned, as indicated by clinical observers and the researches of Madsen and Salomonsen. It merits a trial, as also do the organic preparations of arsenic.

Inhalations of oxygen are advised by Osterwald for the spasms.

General Measures

Feeding.—All food given by the mouth should be in fluid form, so as to be easily swallowed, and this should in severe cases be kept as small in amount as possible, as there is danger of foreign body pneumonia and of exciting convulsions. Rectal feeding should be used to supplement mouth feeding. The tendency to spasm of the sphincter aids the retaining of the injection. As much as 2 or 3 pints may be retained daily. Leyden suggests as a combination 500 c.c. milk, 50 gm. nutrose, and 1 teaspoonful salt. To this brandy and tincture of opium can be added.

Feeding through a soft rubber catheter passed to the stomach by the nostrils is often necessary. Sometimes, owing to spasm, the tube will not pass. Chloroform inhalations will then be necessary. Sometimes it is easier to pass a small stomach tube by the mouth. Subcutaneous injections have at times been resorted to. Olive oil and 10 per cent solution of grape sugar have been employed, also normal horse serum. As much as 500 to 1,000 c.c. can be given. Before passing a nasal tube for feeding or giving an injection in the bowels, or doing anything which might cause a convulsion, it is well to give a dose of morphin, so as to lessen the irritability.

Nursing.—Every noise possible should be eliminated, and the room should be somewhat darkened.

A water-bed will make the patient more comfortable, and prevent to some degree the starting of spasms.

Results of Treatment.—The most acute cases have a very high mortality. The longer the incubation and the slower the onset the better the results. If every case were given an intravenous injection of antitoxin at the time of diagnosis, and treated well in other respects, probably 50 per cent would recover.

Preventive Treatment in Detail

This consists in the use of antitoxin and the treatment of the wound. The instructions printed for hospital internes by Berghausen are so good that I repeat them:

"1. All perforating, penetrating, or lacerating wounds contaminated directly by soil or manure, especially those contracted in the streets or about stables.

"2. All blank cartridge and giant-cracker perforating and lacerating wounds."

INSTRUCTIONS

"1. In all cases above mentioned remove the clothing and foreign material about the wound.

"2. Cleanse the surrounding parts with green soap, alcohol, ether, and sterile water.

"3. Remove with sterile forceps any foreign material lying superficially in the wound.

"4. Cleanse the wound with 5 per cent phenol (carbolic acid), 0.5 per cent hydrochloric acid solution.

"5. Enlarge the opening by free incision if necessary, to cleanse the wound thoroughly, or for the removal of foreign substance.

"6. Use a general anesthetic whenever indicated.

"7. Pack the wound lightly with gauze soaked in the phenol-hydrochloric acid solution, and dress. Change the dressings daily.

"8. Immediately after dressing the wound on the first day give 1,500 units of antitetanic serum subcutaneously.

"9. A careful record must be kept of each case when the patient is discharged."

In case of doubt or on the appearance of symptoms resembling tetanus an injection of 20,000 units of antitoxin should be made at once. When the diagnosis is certain it may be too late. If it is tetanus the symptoms will become manifest in spite of the antitoxin, but will probably not develop to an alarming extent.

Treatment of Actual Cases

This disease is so rare that few physicians see more than one or two cases. The following reports, giving treatment of various kinds and results, are given, because in this way a clearer idea can be obtained than from the general consideration already given. The use of the intraspinal in connection with an intravenous injection has displaced all other methods and is described under the serum treatment of tetanus. Several cases are reported at the end of this series.

Two Moderately Severe Cases of Slow Development Treated with Antitoxin and Sedatives, One Case Having Two Relapses

Case I.—Boy, aged 10; admitted with history of injury 12 days previously. On ninth day rigidity of muscles of lower jaw developed with slight convulsive seizures. On the twelfth day, when admitted, was subject to repeated convulsions lasting sometimes a few seconds and sometimes 10 minutes. During the next five days there were each day 8 to 15 severe convulsions. The first relaxation of the jaws took place on the sixth day of treatment. On twelfth day patient ceased to have convulsions and recovery was uninterrupted.

Treatment.—On each of the first five days 2 doses of 3,000 units of antitoxin were given subcutaneously; on the next two 3,000, and on each of the next five 1,500, a total of 43,500 units in all. Pint enemas of normal salt solution were given daily at first, and patient was fed through a tube. Chloral and sodium bromid, each 10 gr., and morphin, ⅛-gr. doses hypodermically, were given as required. On admission the wound was carefully treated.

Comments.—The first dose of antitoxin should have been at least 10,000 units, and should have been given one-half intravenously and one-half intraspinally. A second intraspinal injection 12 to 18 hours later would have been of value. The immediate giving of the intravenous and intraspinal doses is a most important point and should be insisted on.

Case 2.—A moderate attack with two severe relapses. This case, reported by Fink, is similar to one treated by me six years ago. The patient, 20 years old, was admitted ten days after infection of a sore with cow manure. His temperature and pulse were normal, but the spasms severe. When the spasms were very severe injections of morphia were given, and occasionally inhalations of chloroform. Chloral, 20 gr., and sodium bromid, 30 gr., in mixture, were given every 3 hours. Antitoxic serum was given. After four days the spasms became less, and ceased after another four days. Four months later he had a second attack, and after two months a third attack.

In this case there were probably some remaining spores which developed after the antitoxin administered and that elaborated in the person had been eliminated. In the case that came under my observation I gave an injection of 1,000 units every two weeks for three months after the third relapse.

Two Cases of Tetanus Treated by Subdural Injections of Magnesium Sulphate—Cases 3 and 4

Case 3.—On September 28, 1911, Ronald R., aged 9 years, complained of feeling ill, and did not go to school. The following morning the patient had a violent tetanic seizure, and was ordered to the hospital. He was admitted at 1 P. M., the temperature being 99.4; pulse 112.

The boy had been in the habit of running about barefoot, and there were several small cuts and abrasions on both feet. The cuts were carefully cleaned, and then swabbed with tincture of iodin, and a gauze dressing applied.

As soon as the wounds had been dressed the boy was put to bed, and 1,500 units of antitetanic serum given subcutaneously. At 3 P. M. the patient had a tetanic seizure which lasted two or three minutes; risus sardonicus was well marked, and from this time on there was great difficulty in opening the mouth.

Similar attacks occurred at 4 P. M. and at 5.15 P. M., and a second dose of 1,500 units of serum was then given. The temperature had risen to 100.2°. The attacks now recurred with increasing frequency, until they were almost continuous.

At 2.30 A. M. a third dose of 1,500 units of serum was injected, and under chloroform anesthesia the spinal canal was punctured between the third and fourth lumbar vertebræ and 2.5 c.c. of cerebrospinal fluid was withdrawn, and there was slowly injected in its place a like amount of sterile 25 per cent solution of magnesium sulphate.

After the injection of the magnesium sulphate the patient slept quietly for an hour, and then quite suddenly the breathing became embarrassed, and the temperature fell to 97. As the breathing became steadily worse, a small hypodermic of strychnin was given, and repeated in half an hour's time. The boy's condition distinctly improved, and he took liquid nourishment well.

At 10 A. M. on September 30 the temperature rose rapidly to 104.6°; cold sponging was resorted to, and the temperature fell to 100°. The boy slept all the afternoon, and seemed on the high road to recovery, until the early hours of October 1, when the temperature again rose to 104°. Cold sponging now had no effect on the temperature, and the breathing again became very embarrassed. Strychnin was administered and oxygen given, but the boy's condition gradually became worse, and he died at 10.40 A. M., the temperature immediately before death being 107°.

From the moment the magnesium sulphate was injected to the time of the boy's death no trace of tetanic spasm occurred.

The dose recommended is 1 c.c. of a 25 per cent solution for every 25 pounds of body weight, but from the effect of the drug in this case I am inclined to think this dosage too large. A large dose of antitoxin, given intraspinally, might have been of use in this case.

Case 4.—On November 9, 1911, Vera H., aged 8 years, while running about barefoot, cut her foot on a stone. The wound was treated at home until November 22, when the child, who appeared to be out of sorts, was brought to the hospital.

On admission temperature and pulse were normal. The foot was soaked for 20 minutes in 1:4,000 solution of mercury perchlorid, and then dressed with a boric acid fomentation.

The patient was put to bed and slept well all night, but at 7 A. M. on November 23 she had slight muscular twitchings and complained of pain in the back and of difficulty in opening the mouth; 1,500 units of antitetanic serum were given subcutaneously, and the wound on the foot swabbed with tincture of iodin. Five gr. of potassium bromid were given every three hours.

The muscular twitchings continued at intervals all day, and the temperature rose steadily, until at 5 P. M. it had reached 104°. Under chloroform anesthesia 1,500 units of antitetanic serum were injected into the subdural space, an equal quantity of cerebrospinal fluid having previously been withdrawn.

The tetanic symptoms persisting, a hypodermic injection of 1/16 gr. morphin was given. As the bladder was distended, the catheter was passed, 20 ounces of urine being withdrawn. The patient passed a restless night, and the following morning (6.30 A. M.), under chloroform anesthesia, 1 c.c. of a 25 per cent sterile solution of magnesium sulphate was injected into the subdural space.

This procedure was followed by a distinct improvement, and the muscular spasms ceased until noon, when they recurred with increased violence and frequency. A second hypodermic injection of morphin was given with great benefit, the child becoming quieter, getting a fair amount of sleep, and taking nourishment well.

At 10 P. M. the convulsions returned, the attacks coming on about every hour till 4 A. M., when they ceased, and the child slept till 7 A. M. Severe attacks of tonic and clonic convulsions then came on, recurring every few minutes throughout the day. More morphin was given, but had no effect.

At 4 P. M. a frightful attack of convulsions took place, the body being violently jerked about the bed, and death ensued ten minutes later.

The patient suffered from retention of urine the whole time she was in the hospital, and the catheter was passed as required. During the 48 hours preceding death the temperature was high, and cold sponging was resorted to frequently, and seemed to have a very soothing effect. Immediately before death the temperature rose to 108.2° F.

In this case the amount of antitoxin as in the first case was much too small and should have been given both intraspinally and intravenously.

A Case in Which Treatment Given was Antitoxin and Chloretone

Case 5.—Acute tetanus; recovery. Male; white; aged 10. Incubation, 10 days; duration, 16 days; splinter in foot.

On August 5 the patient ran a splinter into his foot; the wound was dressed and apparently healed in two or three days. Patient was first seen by me on August 17, at which time there was difficulty in opening and closing the jaws. Two days previously he had noticed some slight stiffness and pain on opening the mouth. He was immediately admitted to the hospital at 2.50 P. M. as a tetanus patient. The temperature on admission registered 102.5°. Though apparently healed and hard to find, the place of injury was opened and a piece of tissue removed and wound thoroughly cauterized. A splinter was found imbedded in the tissue over half an inch in length. Under ether anesthesia 3,000 units of antitoxin were given intraneurally into the sciatic nerve of the leg below the groin, and 3,000 more intravenously by the median basilic vein of the arm. The symptoms continued to increase steadily with rigidity, convulsions, arching of back, and rising daily average temperature, and dis-association of the normal pulse and respiratory rhythm up to the tenth day of the disease. The condition of the patient at this time was decidedly serious. On the eleventh day (day beginning at 3 P. M.) the temperature had risen to 104.5° F., pulse 156, respiration 38, and remained with small change at this point until 4 A. M., when a marked change occurred for the better, the temperature falling 4.5° to 100° F., pulse 116, and respiration 24 per minute, the first material fall of temperature, pulse, and respiration since the third day of the attack. The improvement in the general condition continued until, on the sixteenth day, the temperature touched normal, pulse 96, respiration 18. Decreasing stiffness and irritability continued for some days later. The last convulsion was recorded on the twelfth day. From the splinter were recovered classical tetanus bacilli, which caused tetanus in guinea pigs. From the time of the ether anesthesia until the eleventh day, as occasion required, chloretone was given in solution by rectal enema in 30-gr. doses. Complete relaxation followed each dose, lasting from 8 to 16 hours, during which time the patient slept quietly. Antitoxin was given daily subcutaneously in doses of 3,000 units. Liberal nourishment was supplied by nutrient enemata and stomach tube feeding. Saline solutions with frequent laxatives were used to promote elimination by the skin and kidneys.

Case 6.—F. D., girl, aged 10 years, seen in consultation with Drs. W. B. Anderton and A. A. Smith, fell, striking her forehead on the ground, receiving a lacerated wound ¾ inch long over one brow. This was properly disinfected and sutured, healing promptly. Seven days later there was a facial paralysis on the side on which the wound was received. Thirty-six hours later, the jaws were firmly locked. Eight hours after this symptom was noted, the patient received 3,000 units of antitoxin intraspinally and 10,000 intravenously. Several subcutaneous injections were later given. The tetanic spasms were largely confined to the muscles of the jaw and pharynx and, later, the abdominal muscles; attempts at swallowing and the slightest external irritation caused contractions of the muscles of the throat and larynx, cyanosis, general convulsions and unconsciousness. Such convulsions occurred on fifty or more occasions, together with innumerable minor spasms. Pneumonia developed later, resolution being very long delayed. After a protracted convalescence and extreme emaciation, the patient made a perfect recovery.

Case 7.—Thomas B., laborer, was admitted April 1, 1914, to the New York Hospital, with multiple lacerations of scalp and traumatic amputation of toes of the right foot. The wounds were immediately disinfected with iodin and irrigated with iodin solution. The following day, amputation of the toes was performed. April 10 (incubation 9 days), there was slight stiffness of the jaws, which was not reported until the following morning. April 11, 1,500 units of antitoxin were given in the tissues about the wound and 3,500 intravenously; later on the same day, 3,000 units into the tissues about the wound and the same amount intravenously. April 12, the patient was very much worse, and was given 13,000 units intravenously, 8,000 intraneurally and 7,000 into the tissues about the wound. April 13, his condition was still more unfavorable. There was marked opisthotonos. Eight thousand units of antitoxin were given into the spinal canal and 9,000 intravenously. Following the intraspinal injection the temperature rose to 105°; there were severe headache, convulsions and semicoma. April 14, the patient was comatose throughout the day. April 15, the patient was conscious, and there was less rigidity. April 16, there was much less rigidity; and the patient swallowed fairly well for the first time. The patient continued to improve and was discharged cured, April 30.

Comment.—Through a series of misunderstandings, this patient received still further intravenous injections of antitoxin following the intraspinal dosage, although an examination of his blood showed a tremendous antitoxic content. How much credit should be given the single intraspinal dose for the recovery in this case it is difficult to say. It is to be noted, however, that the first real improvement followed shortly after its administration.

CHAPTER XXI

TREATMENT OF DIPHTHERIA

Archibald J. Dickson and William H. Park

Cases of diphtheria may be divided into mild, moderate, severe and malignant for the purposes of treatment. No description is necessary for the first two groups. The severe type includes laryngeal diphtheria, cases occurring in the course of other acute infections, cases showing a nasopharyngeal and nasal involvement, and cases showing exudate on both tonsils extending to the uvula and soft palate. In the latter cases the tissues of the throat may show such marked swelling and edema as to be mistaken for peritonsillar abscess. The malignant type presents marked glandular involvement with frequently a pale waxy appearance of the skin. Dullness and apathy without any delirium are usually present. The laryngeal diphtheria is marked by dyspnea and restlessness. It may be an extension from the pharynx or it may be the primary site of the infection. The dyspnea is usually inspiratory in type, though if the membrane extends to the trachea and bronchi it is sometimes expiratory as well. Gover, in a series of cases examined with Jackson's laryngeal speculum, found that where the membrane was confined to the larynx the exudate was usually more filmy in character than in the other types of cases and adhered less tenaciously and, in wiping it off with swabs under direct vision, there was not much tendency to bleeding.

Treatment

Antitoxin.—The sole action of antitoxin is the neutralization of the diphtheria toxin. The antitoxin should therefore be given in a way and in sufficient amount to accomplish this object at the earliest possible moment.

Antitoxin should be immediately administered to every case, except when it is of the very mildest type, in which there is any suspicion of a diagnosis of diphtheria. Do not wait for the return of a culture, but give the antitoxin early. This admonition applies to all types in which there is believed to be any element of danger and may be the means of saving the patient. A large percentage of the mortality in diphtheria occurs in cases which have received antitoxin late in the disease. It has been our practice to give only one injection of antitoxin and that one should be large enough to control the disease. The antitoxin remains in the body for a number of days. Mild and moderate cases receive subcutaneous or better intramuscular injections; the severe and malignant cases receive intravenous injections. The site of injection is sterilized with tincture of iodin or other disinfectant and some portion of the body where there is an abundance of loose cellular tissue is selected. In intramuscular injections the thigh is a suitable location and does not interfere with the patient's turning in bed.

Intravenous Injections.—In intravenous injection the median basilic vein, or in young children the external jugular vein, is selected. A Burroughs Welcome syringe (5 c.c.) and a No. 9 steel needle are used. The antitoxin is warmed to body temperature and then drawn into the syringe. To be sure that the needle has entered the vein, withdraw the plunger until blood shows in the rack of the end piece and then inject slowly. Intravenous administration is used in all severe and malignant cases to obtain the full value of the antitoxin at once. A suitable preparation produces no untoward effects in children as a rule for, if chills do occur, they are much less severe than in adults. Chills were present in 7 per cent of cases of children four years of age and under. In adults, severer and more frequent chills with nausea and vomiting happen, but the desirability of introducing the antitoxin directly into the general circulation more than offsets these effects in seriously ill cases. Thomson at the Willard Parker Hospital had a series of over 3,000 cases, adults and children, in which he had no untoward effects, but since then one death has occurred. Antitoxins of high potency were used, as in this way the amount injected is lessened considerably.

The effects of intravenous administration are striking in many cases. The temperature falls more quickly to normal and the patient loses his toxic appearance in a shorter time. His condition improves rapidly and it is difficult to keep him at rest as he feels so much better. The effect on the exudate is seen in a much shorter time and it begins to curl up and disintegrate sooner. The glandular swelling also subsides more quickly.

The single dose is advocated because antitoxin remains in the body fluids for many days. The greater the concentration in the blood, the more rapid is its escape from the capillaries into the tissues and the quicker its contact with the toxin. If 20,000 units are given in one dose, the whole amount is immediately effective. If this amount is divided into three doses and the second and third are given after an interval of eight hours, there is acting during the first eight hours only one-third of the required amount; during the second eight hours two-thirds of the total amount is available, and only at the end of sixteen hours is the patient having the effect from the whole amount. There is no objection to giving a second dose if the first is thought insufficient. The harm done by giving an insufficient first dose cannot, however, be removed by doing this. Diphtheria antitoxin requires at least two weeks to be eliminated.

Influence of Size on Dosage.—Diphtheria antitoxin influences diphtheria solely through its ability to neutralize diphtheria toxin. To do this the two substances must come in contact.

The diphtheria toxin is mostly located at the site of the diphtheria. In toxic cases some of the toxin has been absorbed and has been carried by the lymph vessels to the general blood supply and later distributed throughout the body. The amount of toxin in the body even in the most malignant case requires but a relatively small amount of antitoxin to neutralize it. Probably 100 units would be more than sufficient. The difficulty is to convey the antitoxin to the cells which are being attacked by the toxin. To reach these, the antitoxin must first enter the bloodstream and then pass from the capillaries to the tissues. Only a very small proportion of the antitoxin in the blood as it passes through the capillaries passes through their walls to the tissues. It is necessary, therefore, to throw into the blood a great excess of antitoxin, so that there will pass to the tissues in a short space of time sufficient antitoxin to neutralize the toxin.

It is, therefore, the amount of antitoxin in a cubic centimeter of the circulating blood rather than in the whole blood supply that is of importance. The dose, therefore, should be proportional to the weight. A child of fifty pounds should receive twice as much as a child of twenty-five pounds. There are certain reasons, however, which cause us to modify this rule and give larger doses to the smaller children. Diphtheria antitoxin has no deleterious effect except that due to reactions which follow from the horse serum in those who are sensitive. The serum reactions are less in very young children. Furthermore, the danger from diphtheria in very young children is greater than among older children. Because of these reasons we advise that little children receive about one-half or one-third the amount that is given to adults.

The dosage we have adopted in the New York City contagious disease hospitals is given in the table. There is no objection to giving somewhat larger doses. When the exudate does not disappear within forty-eight hours, it is wise to think of some other process, such as Vincent's angina or syphilis.

Administration of Antitoxin.—*The earlier the remedy is administered the more certain and rapid is the effect.* In cases of any severity where diphtheria is suspected, and in cases of croup, it is far better to administer the remedy at once, making a culture at the same time, than to delay the treatment until a diagnosis has been made by bacteriologic examination. The first injection should be large enough to control the disease. One large dose given early is far more efficacious than the same amount in divided doses. Severe cases and those in which the administration of antitoxin has been delayed, or cases which are progressive because of an insufficient first dose, should be given a large intravenous injection whenever feasible. In this way the *full value of antitoxin is obtained at once* (see chart, Fig. 1), wheras the absorption from the subcutaneous or intramuscular injection is so slow that many hours must elapse before

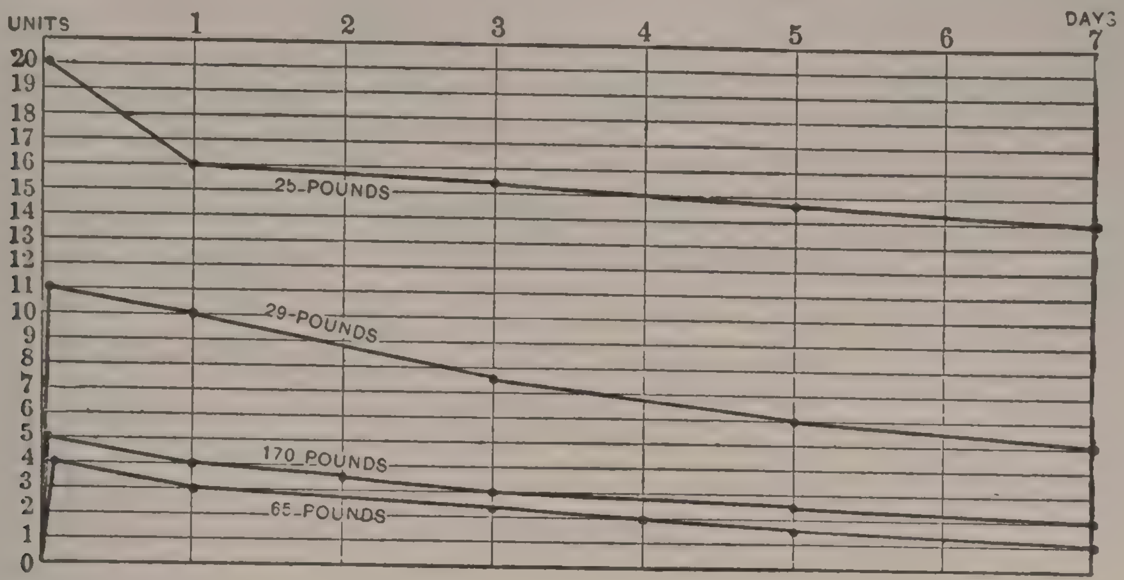

FIG. 1.—CHART SHOWING UNITS OF ANTITOXIN IN 1 C.C. OF HUMAN BLOOD AFTER AN INTRAVENOUS INJECTION OF 10,000 UNITS. Note the smaller children show the greatest amount of antitoxin in the blood.

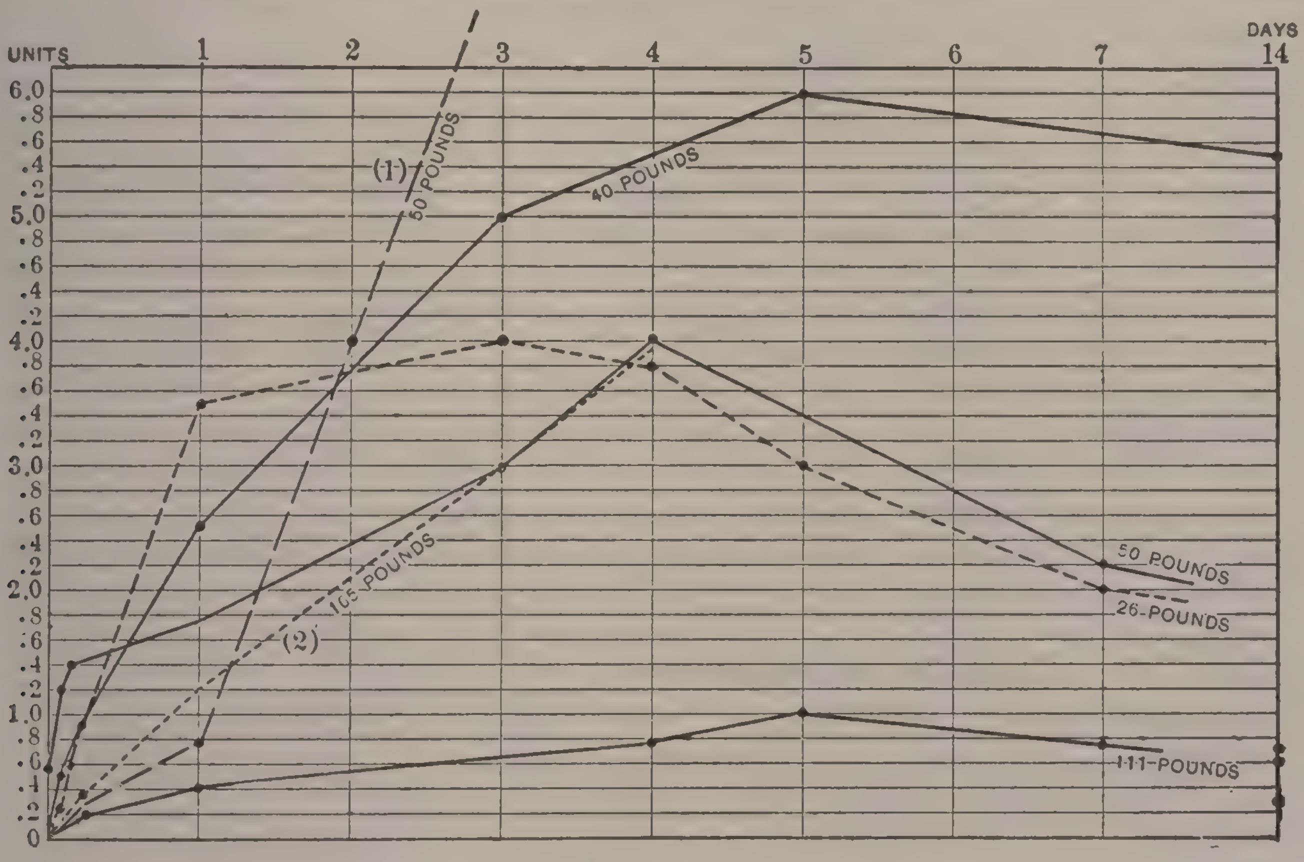

FIG. 2.—CHART SHOWING EXTENT AND RAPIDITY OF ABSORPTION OF 10,000 UNITS OF ANTITOXIN GIVEN SUBCUTANEOUSLY OR INTRAMUSCULARLY. Each line represents the antitoxin content of 1 c.c. of blood at different intervals of time in a different patient. Compare with Fig. 1. The patients Nos. 1 and 2 showing the greatest amount of antitoxin produced antitoxin early in the attack and so added their own antitoxin to what was absorbed.

any great amount of antitoxin has found its way into the general circulation (see chart, Fig. 2). It must be warmed to the body temperature and given very gradually.

AMOUNT OF ANTITOXIN REQUIRED IN THE TREATMENT OF A CASE

Patients	Mild Cases	Moderate	* Severe	* Malignant
Infants, 10 to 30 lbs. in weight (under 2 years of age).....	2,000 units to 3,000 units	5,000 units to 8,000 units	6,000 units to 10,000 units	10,000 units to 15,000 units
Children, 30 to 90 lbs. in weight (under 15 years of age)..	3,000 units to 5,000 units	5,000 units to 10,000 units	10,000 units to 15,000 units	14,000 units to 20,000 units
Adults, 90 lbs. and over in weight....	4,000 units to 5,000 units	5,000 units to 15,000 units	15,000 units to 20,000 units	20,000 units to 40,000 units

* One-half the amounts stated given intravenously.

Cases of laryngeal diphtheria, moderate cases seen late at the time of the first injection, and well-defined cases of diphtheria occurring as a complication of the exanthemata should be classified and treated as "severe" cases.

In all cases a single dose of the proper amount, as indicated in the schedule, is recommended.

It is recommended that the methods of administration be as follows:

Mild cases—subcutaneous or intramuscular.

Moderate cases—intramuscular.

Severe cases—intravenous for at least one-half of the amount, intraperitoneal, or intramuscular for the remainder.

Malignant cases—intravenous for at least one-half of the amount.

Some point on the surface of the body should be chosen for the injection, as where there is an abundance of subcutaneous, or muscular tissue, the abdomen or infrascapular region. Before the remedy is administered, the skin should be sterilized at the point of injection with tincture of iodin or other disinfectant. The syringe should be thoroughly sterilized. It is better not to employ massage over the point of injection.

Anaphylaxis.—The danger of the administration of antitoxin to a patient who has previously been injected has possibly been overemphasized and the medical profession has been as a whole fearful of the phenomenon known as anaphylaxis. The introduction of a second dose of antitoxin at any time subcutaneously or intramuscularly is practically free from danger. The only possible danger is that the needle may enter a vein and most of the serum get immediately into the general circulation—an extremely remote possibility. Many hundreds of cases under our care have been given a second administration of antitoxin within a period of from three to four weeks after the first dose (the most susceptible time for anaphylaxis) and we have not seen any bad results. Given intravenously extreme caution must be exercised, especially if the former injection was of recent date. After an interval of from six to ten months the danger of giving a second dose is materially lessened. The symptoms appear almost immediately, the patient showing great swelling of the lips and face, edema, cyanosis, labored breathing and a rapid, thready pulse. Collapse and death supervene in a very few cases. The treatment for these cases is the injection of a dose of a 1:1,000 dilution of adrenalin into a vein without delay. In severe and malignant cases having a history of asthma or of a previous injection of serum where intravenous administration is indicated, fractions of a cubic centimeter of antitoxin well diluted may be given at intervals of ten minutes intravenously. Should no ill-effects occur after six doses thus given, then administer enough antitoxin to control the disease.

Local Treatment.—As a rule most cases of diphtheria do not require any local application to the throat, for as soon as the antitoxin becomes effective the membrane begins to disintegrate. The mouth and gums are cleansed with some mild mouth wash as a part of the patient's routine toilet. In cases with edema of the tonsils and uvula, a gentle irrigation of normal saline solution or of sodium bicarbonate (1 dram to the pint of warm water) adds to the patient's comfort. Nasal irrigations are not recommended as there may be some danger of infecting the middle ear. Should irrigation be distressing or fatiguing to the patient, it should be discontinued. Children have to be restrained by pinning in a sheet (mummy dressing), but irrigation for children has been practically discontinued at the Willard Parker Hospital, as their struggling seems to be more fatiguing than the treatment is of benefit.

Treatment of Laryngeal Diphtheria.—In 1918, at the Willard Parker Hospital, the croup cases were examined by means of Jackson's laryngeal speculum. Previous to this time no direct view was attempted and intubation was performed on the clinical aspects of the case. A culture of the larynx was taken through the speculum and the membrane was wiped out by means of the swab. A very high percentage of these cultures was positive, much more than in the cultures taken from the pharynx. This was probably due to the fact that the swab came in contact more thoroughly with the exudate. It was also noted that the cases so treated or examined seemed to breathe better at the time of the examination from the lifting up of the larynx, and some of these were able to go without intubation. Gover reported a series of 189 cases so examined and, while the larynx was swabbed out only once, permanent relief was afforded in a number of cases.

Once a child is intubated, the difficulty of taking nourishment, the increased flow of saliva and consequent coughing tend to lower its resistance and increase the susceptibility to bronchopneumonia; and also about 0.5 per cent of intubated cases become what are known as "chronic tubes." It was noted that some cases which were in need of intubation could be tided over for a space of from six to ten hours after the membrane was removed by means of swabbing; and in addition this interval of time was sufficient for the antitoxin to become effective. If the croup cases can be carried over for a period of twelve hours after intravenous administration of antitoxin, only a small percentage require intubation.

Thomson continued the swabbing treatment of croup cases and repeated the swabbing process as often as the dyspneic symptoms returned and the child could be kept from being intubated. He used small pledgets of gauze on an applicator. Wiping out the larynx results in relief of the dyspnea and cyanosis and the patient usually goes to sleep. In some cases the relief is permanent. Usually the good results last only for a few hours and it is necessary to wipe out the larynx and free it from membrane and mucus.

This procedure does not increase the danger to the patient in any way and bronchopneumonia developed in no case as a result of it. Neither did there seem to be any risk of pushing down the membrane and blocking the larynx or trachea. Aphonia disappeared earlier than it did in intubated cases. The following table shows Thomson's results of applicator treatment.

THOMSON'S RESULTS OF APPLICATOR TREATMENT

Cases	1919	1920
Number of cases of diphtheritic laryngitis..	159	132
Patients neither intubated nor treated with applicator	84	79
Patients intubated	75	16
Patients receiving applicator treatment not intubated	0	37
Total number of deaths..........	42	20
Mortality	26 per cent	15 per cent

Gover and Hardman are using metal perforated suction tubes which are inserted through the Jackson speculum and attached to a Yankauer pump. The membrane and mucus are thus removed by suction. Hardman[1] prefers in some cases a French elastic catheter to the metal tube and it has the possible advantage of causing less injury in unskilled hands. He has also devised an instrument by means of which the catheter can be introduced into the larynx without using a laryngeal speculum—much in the same way as an intubation tube is introduced. A mouth gag is used to prevent the patient from biting the tube and the child can breathe through it. Suction can be attached either by means of a suction pump or by a hand bulb.

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[1] Archives of Pediatrics, March, 1923.

The suction treatment of croup cases decreases markedly the number that need intubation with a consequent lowering of the mortality. The temperature usually falls soon after relief is given. Cases with subglottis edema generally have to be intubated.

Direct inspection of the larynx by means of a laryngoscope differentiates acute stenotic laryngitis from laryngeal diphtheria. The former occurs frequently in measles before the rash has appeared and also in scarlet fever and in other infections such as influenza. In hospital practice this means is especially valuable in preventing such cases from going directly to the croup ward and thus causing a mixed infection. Edema of the glottis, papillomata, syphilis, tuberculosis and foreign bodies may also be differentiated by this means.

Intubation.—The indications which make intubation imperative are: (1) extreme restlessness and dyspnea; (2) cyanosis which tends to become permanent; (3) sweating; and (4) retraction of the chest. Where it is possible the patient should be cared for by a trained tube nurse and carefully watched. These cases have paroxysms of dyspnea and with good nursing may get over successive attacks. Especially is this true in older children, but, if the paroxysms are becoming more frequent, intubation should be done. Never allow the patient to pull until its strength is exhausted and its resistance is lowered. Sternal retraction does not mean so much in young infants as a sign for intubation. Fat children do not do well and should not be allowed to pull long.

Technic of Intubation.—In performing an operation of this kind it is of the utmost importance that the patient be under absolute control. To this end what is known as a "mummy" dressing is used. The patient is wrapped in a sheet, the upper border of which comes to about three inches below the shoulders. The arms are placed parallel to the sides and the sheet is firmly secured by means of large safety pins at the upper border, at the hips and at the ankles.

A Denhardt mouth gag is placed in the left side of the mouth as far back on the teeth as possible, and is *slowly* opened (no gag is needed in infants without teeth). It should be held firmly to prevent slipping and care should be taken not to pinch the child's cheek.

The index finger of the left hand is inserted into the mouth and after straightening out the epiglottis, if it should be curled up, the tip is placed on the arytenoid cartilages. The tube is passed along the palmar surface of the index finger of the left hand and, as soon as the tip of the tube reaches the end of the intubating or guiding finger, the handle of the introducer is raised until it is parallel with the dorsum of the tongue. The tube thus directed by the finger in the mouth is inserted into the larynx without any force being used. Once the end of the tube has engaged the larynx, it is released by the spring on the introducer and the left forefinger is shifted to the head of the tube to facilitate the withdrawal of the obturator. If the tube is in position in the larynx, a characteristic tubal cough is noted, the cyanosis is replaced by a healthy red color of the lips and the dyspnea is relieved. The tube is pushed down until the head of it rests against the arytenoid cartilages.

A linen thread is generally attached to the tube to recover it in case it has entered the esophagus. Should it be in the correct position, however, the thread is unwound and removed. The thread may be secured to the cheek by a strip of adhesive plaster instead of removing it.

Difficulties in intubation are due to insufficient practice on the cadaver and inability to recognize the landmarks by touch. If the patient's head is too flexed it may also hinder the operation. Too much force exerted in a wrong direction makes intubation difficult.

Extubation.—The average length of time a tube is worn is from four to five days. It is removed sometimes a day earlier if there is a normal temperature and the patient is free from coughing. Again it is left in situ if the general condition of the patient is not satisfactory. The administration of drugs or anesthetics before extubation does not seem to have any beneficial effect in helping to keep the patient from reintubation.

The technic of extubation is much the same as intubation. The index finger of the left hand locates the head of the tube in the larynx and acts as a guide for the extractor to follow. Keep the tip of the extubator against the palmar surface of the index finger of the left hand till the head of the tube is reached. Then raise the handle of the extractor till it is parallel with the dorsum of the tongue. When the tip of the instrument is well in the lumen of the tube, press the lever on the extractor and raise it. As this is done, place the left finger behind the head of the tube to facilitate its removal. Be sure that the tip of the extractor is in the lumen of the tube before pressing the lever, as otherwise the larynx will be lacerated.

Intubation and extubation require only a few minutes for their skillful performance. Two admonitions must always be kept in mind—*don't hurry* and *use no force.* It is better to make several brief attempts if necessary rather than obstruct the patient's breathing by keeping the finger in the mouth for too long a time. Should vomiting occur while intubating or extubating the mouth, the tube, etc., must be cleaned before renewing the operation.

Intubation is generally free from any accident. Sometimes laceration of the tissues occurs from too great force applied in the wrong direction and a false passage is made. This is usually through the ventricle of the larynx. Rarely does the larynx relax so that the tube slips down into the trachea. Tracheotomy is then necessary to recover the tube. Occasionally the head of the tube sinks down below the arytenoids but not through the cords. In such cases it is almost impossible to remove it with the ordinary extubator. The French method of extubating by grasping the larynx externally and flexing the head will not succeed. With the laryngeal speculum a long steel applicator with a small hook on the end just sufficient to pass through the lumen of the tube is introduced. The hook catches the lower end of the tube and allows its removal.

Children under two years of age do not do well when intubated. Children over three years do much better—70 to 80 per cent recovering. Fifty per cent of intubated cases which get well do so with one intubation, 40 per cent require two intubations, 8 per cent three or more intubations, 1½ per cent repeated intubations, and ½ per cent become chronic tube cases in a large croup service.

In all cases needing reintubation there is some pathological condition of the larynx which necessitates it. Nervousness plays a very small part. Cases which have a tendency to repeated coughing up of the tube should either be intubated with a Lynah non-cough-up tube or have a tracheotomy performed. In the latter event it must be remembered that a complete closure of the larynx above the tracheotomy may occur and must be combated by dilatation.

Cases of retained tubes are due to the formation of a stricture in the neighborhood of the cricoid cartilage. They tax the skill and resourcefulness of the most expert and take a long time to cure. Their treatment consists in dilatation, removal of webs and polypoid tissue, secondary tracheotomy and laryngostomy.

Tracheotomy.—Tracheotomy in croup cases is performed under local anesthetic or in very urgent cases without any anesthetic. Chloroform or ether should never be used.

In performing this operation the patient is placed in the recumbent position with a sandbag under the shoulders and the head extended over the end of the table, and held firmly in direct line with the body. An incision from just below the cricoid cartilage to the suprasternal notch is made, cutting through skin and superficial fascia. Retractors are introduced and the deeper fascia divided by means of shallow incisions till the rings of the trachea are exposed at the upper end of the incision. Push aside or ligate any veins that may come to view and shove down the isthmus of the thyroid gland. The tracheal rings should be cut in the median line and as low down as possible. Do not cut the cricoid cartilage as it tends to produce a stricture which is later difficult to deal with. Insert a tracheal dilator into the opening in the trachea and then the tracheotomy tube. Emergency tracheotomy requires that there is no time to be lost in making nice separation of the tissues. The head is extended as before and the surgeon grasps the larynx with the thumb and second finger of the left hand to steady it and keep it in the midline while he boldly cuts through all the tissues to the trachea. He inserts the index finger of the left hand into the incision and uses it for a guide on the rings of the trachea as he cuts them. Artificial respiration should be done at once if the patient is not breathing. Amyl nitrite and oxygen are the best respiratory stimulants and should be used.

The after care of tracheotomy cases is important. After the tracheotomy tube is fastened in position by means of tape tied around the neck, a bib of oiled silk and gauze is attached to the tape to keep the mucus and secretion from soiling the wound. A piece of gauze moistened with warm boric acid solution is laid over the tube to act as a filter and to warm the inspired air. The secretion must be wiped away before it is sucked back into the tube. The bib and the gauze filter are to be changed as soon as soiled. The inner cannula is cleaned as often as is necessary to keep it unobstructed. The outer tube should be changed by the physician once a day. The wound should be kept as clean and free from secretion as possible. In cleaning the cannulæ, be sure that all the gummy secretion has been removed and that the lumen is perfectly free.

The patient is ready for decannulation when he can breathe with the tube tightly corked. The wound is then packed with gauze so that it begins to heal first at the bottom.

General Treatment of Diphtheria.—Next to the administration of antitoxin, rest in bed is the most necessary treatment. Muscular exertion of any kind is to be avoided and a nurse trained in the care of these cases should be employed. It is hard to make some patients realize the importance of remaining quiet. In mild cases, rest in bed for about ten days is the usual rule. Severer cases are kept in the recumbent position as long as the heart sounds show any weakness. Cases with paralysis may be confined to bed for months. The importance of rest and quiet cannot be too strongly stressed.

The diet for the first few days consists of milk, cereals, broths, junket, etc. As improvement occurs, it may be made more generous. In intubated cases under one year of age it may be necessary to feed with a formula appropriate to the age. This is given a few drops at a time by means of a medicine dropper with the child flat on the back.

Complications.—The mild and moderate cases are usually free from any serious complications. The most frequent are some irregularity in the pulse rate or tachycardia. In the more severe forms of the disease all kinds of paralyses occur. The commonest is palatal which comes on early. Then, too, paralysis of the accommodation of the eye is frequent. Later in the illness paralyses of the pharynx, larynx, esophagus and of the diaphragm may come on. Gavage will be necessary for the esophageal paralysis and good results have been reported from the use of the pulmotor in diaphragmatic paralysis. The breathing is costal in type with the involvement of the diaphragm, and only half of it may be attacked. Bladder paralysis is very rare and requires catheterism sometimes for several weeks. Facial paralysis occurs occasionally. General peripheral multiple neuritis comes on late in the disease, usually in the fourth or fifth week. The extremities are usually involved and it takes weeks before they recover. The muscles of the neck may be paralyzed so that the patient is not able to hold his head up, or the muscles of the trunk may be affected and he is unable to turn in bed. These peripheral paralyses take many weeks to get better.

Sensory disturbances also are manifested in diphtheria. Numbness and tingling of the fingers and toes are frequently found in severe cases.

The chief danger of diphtheria is heart failure and this may occur early in the illness or late. If early it is usually in the first week and is ushered in by nausea and vomiting. The pulse drops down to even as low as 18 to the minute, and soon becomes imperceptible at the wrist. The heart's sounds lose their muscular character and become toneless. The hands and feet become cold, and the patient cyanotic. The mental condition is clear and there is usually no pain. Cardiac stimulants have not been of much benefit in our experience, but small doses of morphin hypodermically have seemed to help.

Bronchopneumonia is the chief pulmonary complication and is seen generally only in the laryngeal type of the disease, but it may occur from aspiration where there is pharyngeal paralysis.

Albuminuria is common. Nephritis is rare. Hemiplegia sometimes occurs. Loss of knee jerks is quite common. Adenitis is present in all very toxic cases but practically never goes on to suppuration. The intense swelling of the throat and tonsils has frequently been mistaken for peritonsillar abscess and been incised. Otitis media and mastoid are rare complications. Epistaxis is fairly common in nasal and toxic cases of diphtheria. Pretracheal abscess occurs occasionally in intubated cases even under the most competent intubator.

Diphtheria carriers are troublesome to treat. Irrigations and applications of all kinds have been advocated and tried, but the best results have followed the removal of the tonsils and adenoids. Cleansing the nostrils with warm normal salt solution is of some value. When possible the carriers should be out in the air and sun. The use of the X-ray on the tonsils has lately been advocated. It is too soon to determine the results.

SPECIFIC PROPHYLAXIS IN DIPHTHERIA

William H. Park

There have been a number of discoveries which have led up to our present perfected methods of preventing diphtheria. The discoveries of Klebs and Loeffler led to the detection of the diphtheria bacillus and paved the way for Roux to discover the diphtheria toxin and Behring and Wernicke the antitoxin.

Experimental toxin immunization, at first confined to animals, was later used successfully in man. The diseases due to the microbes which produce the strong soluble toxins, such as diphtheria, tetanus and botulism, are peculiar in the fact that, if the effect of the toxin can be neutralized, the disease comes to an end unless damage has been excessive, and also that they cannot attack persons who have antitoxin in the body fluids. These bacteria are also prevented from infecting those who have general protective or bactericidal properties in their blood.

A person may thus be immune from diphtheria because of the possession of antitoxin or general protective substances. The majority of persons who develop diphtheria begin to recover before there is any appreciable amount of antitoxin. In fact about two-fifths of the persons who recover from diphtheria never develop antitoxin because of the attack. These are apt to be the more severe cases. While the general protective substances are very important, we have no practical method of causing their development. Injections of dead diphtheria bacilli were tried by Park and Zingher in human beings without success. We are confined, therefore, to the use of modified toxin and antitoxin.

Immunization through Antitoxin

The use of toxin injections in non-immunes is valueless in the presence of infection as the immunity does not develop until four weeks or later. For this purpose the use of antitoxin is necessary. It is estimated that, when the blood contains over one-fiftieth of a unit of antitoxin in each cubic centimeter, an individual is practically safe from diphtheria. In an institution housing many hundreds of children, I administered to each child 300 units with the result of immediately stopping an outbreak of diphtheria. In an insane asylum owing to the development of 50 cases within two days, we gave each of the 3,500 inmates 1,000 units. No further cases developed.

The New York City Health Department has for thirty years advocated the injection of 1,000 units of antitoxin in each inmate of a family in which diphtheria has developed and it has given these injections to many thousands. Among the first 10,000 children injected, there were 25 that developed suspicious infections. Not one of these was severe. If exposed children are known to have a Schick negative reaction, they do not need an injection of antitoxin.

Diphtheria antitoxin being made by the horse is a foreign substance in man. For this reason it is eliminated after a few weeks. It is shown by experience in the presence of infection and by means of the Schick test that the immunity following an injection of 500 units lasts from ten to twenty days and one of 1,000 units from fourteen to about twenty-eight days. A second, or any later, injection gives an immunity of but little more than half the duration of the first injection. The only cases in which an immunizing dose should be avoided are those giving evidence of the condition of status lymphaticus or a history of attacks of asthma.

Schick Test and Immunization through Injections of Diphtheria Toxin-Antitoxin.—The Schick reaction is so frequently used to determine those who are in need of specific passive or active immunization against diphtheria that it will be described first, and this description will be followed by a consideration of active immunization through diphtheria toxin-antitoxin and passive immunization with antitoxin.

As most laboratory men know, the Schick reaction is a development of the old Roemer immunity test. For a number of years we have used the reaction of the skin of guinea pigs as an index of the degree of neutralization of the standard dose of toxin, by the amount of antitoxin added in testing the antitoxic potency of the serum from horses immunized against diphtheria toxin. The skin is a tissue which holds substances injected into it for a considerable length of time. If, in the injection of the mixed toxin and antitoxin, there is an excess of toxin, the skin of the guinea pig at the spot is irritated. If there is an exact balance or an excess of antitoxin in the mixture, no inflammatory action results and, therefore, no hyperemic spot appears. In our earlier investigations on natural antitoxic immunity in man, we took bleedings from children and adults and tested these for antitoxin by the method just described. This method was so time-consuming that only a few persons could be tested.

The idea occurred to Schick of adopting this animal test so that, instead of taking blood samples from human beings to test whether they had natural or acquired antitoxin, it might be possible to introduce a tiny but definite amount of diphtheria toxin in the skin. If this toxin met, in the skin fluids, an amount of antitoxin sufficient to insure immunity, it would be neutralized, but if there were an insufficient amount of antitoxin, the toxin would be held in the skin more or less unneutralized and, just as in the case of the laboratory animal in which a toxin mixture had been introduced, the skin would be irritated, become congested and a bright red spot would develop. This test was based on the idea that the plasma in the skin contained amounts of antitoxin comparable to that in the blood.

Hundreds of thousands of tests during the past ten years have proved beyond doubt that Schick developed an accurate test for the presence or absence of diphtheria antitoxin in the body. Careful investigation has demonstrated that if the blood contains adequate antitoxin for immunity there will be sufficient in the fluids of the skin to neutralize the Schick dose of toxin. It is evident that, if this test is to be employed, sufficient toxin must be injected to cause irritation if there is no antitoxin or an insufficient amount for protection is present. It is also equally important that an excessive amount should not be given, for then even an amount of antitoxin in the skin sufficient to insure protection would be insufficient to neutralize the overdose of toxin.

Experience has taught that the proper dose of toxin is one-fortieth of the amount that would kill a guinea pig weighing 250 gm. This is given in 0.2 c.c. of salt solution. If we prefer to follow Schick's directions exactly we would give one-fiftieth of a fatal dose in 0.1 c.c. These two procedures produce equal results. The larger amount of fluid spreads the toxin in a larger area of the skin and so meets a larger amount of skin plasma and requires slightly more toxin to give a comparable result. The practical use of the Schick test has shown that errors may readily creep in which are most confusing. The technic of the Schick test is very simple in the hands of the experienced but it must be carried out with the greatest care. The needle should pass between the layers of the skin just enough to cover the opening and so superficially that you can see the needle. If the fine needle penetrates too deeply, the fluid escapes into the adjacent tissue, and, as it is not retained, its proper action on the skin does not develop. All who have seen the Schick test or have performed it know that the sign of the correct administration of the injection is the raised small whitish area, about 5/16 inch in diameter, which develops and remains for some minutes because of the entrance and holding of the fluid in the skin. When this appears, we are certain that the correct technic has been employed.

Reliability of the Schick Toxin.—It was recently learned that many forms of glass cause a deterioration of the diphtheria toxin in contact with it. The laboratory has put the right amount of toxin into the vial or into the capillary tube, but within the course of two or three weeks, the potency of the toxin may have dropped more than 50 per cent. The use by many of weakened toxin naturally has led to conflicting results and has caused some persons to believe that children showing a negative Schick test at one time show a positive test at another. With toxin of uniform strength the results of repeated tests properly carried out on the same persons have shown very great similarity. In fact, after years of experience in following up a number of thousand children, I am convinced that there is a remarkable persistency of antitoxin in those who have developed it. In the course of seven years we have not found a fluctuation as shown by a change in the Schick test in more than 10 per cent of the retested children, and even when it occurs there is some doubt as to whether the toxin which was used was always of equal potency. If we grant, as I think we are justified in doing, that the Schick test is one of great accuracy and that children after the age of three who show a negative Schick test have the promise of a lifelong immunity, what is the value of this test in the prevention of diphtheria? This test is used for a twofold purpose: (1) to give the knowledge of security to those who develop a negative reaction; and (2) to prevent the unnecessary use of the immunizing injections. It certainly is of great value under many conditions to know that a child is immune and for this reason alone the Schick test is well worth while. For instance, a physician found that his wife had a mild diphtheria. He had very recently done a Schick test on his year-and-a-half-old baby. The question was whether to give antitoxin to the baby with the possible development of an annoying rash. The fact that the baby had recently had a negative Schick test made it safe to withhold the serum. Second, the Schick test is of the greatest value as an index of the need of giving the immunizing injections. The importance of the Schick test becomes greater with age, but even in young children between three and six years of age, in which the majority will require the injections, it is still of value because it not only prevents the giving of the toxin-antitoxin to about a third but it gives the knowledge that they are safe, which the injections without a later Schick test cannot give. Many health departments, in order to facilitate the use of the toxin-antitoxin injections, suggest that in children under six and even in older children a Schick test may be omitted. Undoubtedly there are many conditions in which this advice is good, but we must remember that in these children who receive the injections no positive statement can be made that they are immune without a Schick test, so that the earlier Schick test not only saves them from the immunizing injections but also gives the assurance which cannot be obtained without a Schick test.

Technic of Schick Test and the Control Test.—To carry out the test, it is essential to have a good syringe, with a sharp, but short-pointed fine needle. Most persons prefer a needle with a length of 1/4 inch. The usual 1 c.c. "Record" syringe, with a fine platinum-iridium needle, or a 26 gage 1/4 or 1/2 inch steel needle, answers the purpose well. The Health Department furnishes a standard diphtheria toxin contained in capillary tubes in such amount that the contents of one tube added to 10 c.c. of water gives the required dilution. The dilution will keep in the ice-box with little deterioration for at least twelve hours. Some of the biological plants furnish the toxin in vials.

Although the intensity of the reaction varies in different individuals, a well-marked redness indicates an almost complete absence of antitoxin in the individual tested. Faint reactions point to the presence of very small amounts of antitoxin which are not sufficient, however, to protect the individual with certainty against diphtheria, but would probably protect from systemic intoxication.

The Control to the Schick Test.—Among older children and adults there are occasionally cases in which a pseudoreaction to the toxin injection somewhat similar to the Schick test follows this injection, which is due not to the toxin but to the accompanying protein in the solution. This places about 5 per cent of the probably negative Schick reactions in doubt.

To overcome this, immediately following the Schick test an intracutaneous injection of a little more than an equal amount of the heated toxin is given on the other arm. The heat destroys the diphtheria toxin but leaves the protein practically unaltered.

On the fourth day, the reactions on the two arms are noted. Where the control arm is negative and the toxin arm is positive, we are certain that we have a positive Schick reaction.

Where the control arm shows a slight or atypical reaction and the toxin arm a typical reaction we are again practically certain that we are dealing with a positive reaction.

Where both arms show reactions of equal intensity we are compelled to weigh the evidence. If each arm shows only a moderate or an atypical reaction we are pretty safe in assuming that this is only a pseudoreaction. If both arms have similar but marked reactions, we are justified in considering that both may be persisting pseudoreactions but we are faced with the difficulty that a strong pseudoreaction would cover up a true reaction and therefore we must concede that the individual may show a combined reaction and treat it accordingly; that is, we give the toxin-antitoxin injections to produce immunity. The protein or pseudoreaction usually appears earlier than the toxin reaction and generally becomes less marked or disappears before the fourth day.

Often the first Schick test is given without a control on the other arm. This is conceded as less scientific but it only means that 5 or 10 per cent of the reactions are read as possibly positive which would probably have been diagnosed as negative if the control protein test had been available for comparison. The advantage of this method is that it saves the children from the injection of the heated toxin as a control. The disadvantage is that 5 or 10 per cent of the children are injected with toxin-antitoxin unnecessarily.

The control injections should be given to all children at the retest. This is very desirable because otherwise some 5 per cent of the children would always remain doubtful.

My own opinion is that in the older children and adults a control is always advisable; in children under seven in whom the pseudoreactions are less frequent, either method is suitable.

Subcutaneous Injection of Toxin-Antitoxin as a Substitute for the Schick Test.—I have found that if the dose of toxin-antitoxin is injected strictly subcutaneously it will act like the Schick test. Usually at the end of twenty-four hours a reddened area about the size of a nickel or a quarter of a dollar appears over the point of the injection if the person is not immune. Within forty-eight hours the reaction always occurs. The toxin-antitoxin is somewhat more liable to cause a pseudoreaction than the Schick dose of diluted toxin. For this reason it is better to read the test on the fifth, sixth or seventh day by which time the pseudoreaction has usually disappeared. The best place to make the injection is just under the skin of the front of the arm above the elbow. The toxin-antitoxin should be of standard strength; that is, five c.c. should kill a guinea pig in from four to fifteen days. The advantage of the subcutaneous injection is that a diagnostic test is combined with an immunizing injection.

Toxin-Antitoxin Injections.—Since the founding of this country the prevention of diphtheria has occupied the attention of health authorities. The discovery of the diphtheria bacillus and of antitoxin added to our means of preventing it and of stopping the disease when developed. At the present time the death-rate is not more than one-sixth of what it was thirty years ago and, in some localities, not more than one-tenth. The number of cases has, however, been reduced probably not over two thirds. Until three years ago the number of deaths each year in New York remained above 1,200 and the number of cases remained as many as 12,000 to 15,000 annually. Indeed, in many parts of the country, diphtheria has been slightly increasing during the last few years. These facts impressed health authorities and laboratory workers and made them realize that we had accomplished about all that could be hoped for from our present measures and influenced them to welcome a test of the value of active immunization through toxin modified by antitoxin.

Immunizing Results of Injections of Diphtheria Toxin.—It is over twenty-five years since the earliest work was done on the active immunization of small animals by mixtures of toxin and antitoxin. Until then investigations were confined chiefly to the use of toxin injections to stimulate the development of large amounts of antitoxin to be utilized for producing temporary passive immunity in man; but it is only since 1913 that active human immunization has been attempted practically. The researches of Ehrlich on the development of antibodies in animals injected with ricin and abrin led von Behring and Kitasato to investigate the effect of injecting the toxins of tetanus and diphtheria. The results were similar. Animals which developed the specific antitoxins were found to be immune to tetanus and diphtheria. Horses treated by repeated injections of toxin were found to add to their antitoxin with each injection and to accumulate it to such a degree that a few cubic centimeters of their blood contained sufficient antitoxin to immunize persons to whom it was transferred.

The results of experimentation have demonstrated that practically all susceptible animals, including man, can be immunized against diphtheria infection by repeated injections of toxin. Experience has brought us the surprising knowledge that a considerable percentage of several species of animals have in their blood minute amounts of a substance apparently identical with diphtheria antitoxin. It is found that those which possess this natural antitoxin not only receive moderately large and quickly repeated injections of toxin with safety, but also respond quickly to the toxin stimulus and make additional large amounts of antitoxin. Those which have no natural antitoxin are both extremely sensitive to the poisonous action of the toxin and slow in responding to the injections in their production of antitoxin. The long time and the great care required to immunize with unaltered toxin and the rather severe local reactions prevented its practical use for immunization purposes in man.

Use of Toxin Modified by Antitoxin for Active Immunization in Animals.—The earliest knowledge that injections of toxin almost neutralized by antitoxin are capable of stimulating in animals the production of antitoxin came quite accidentally. As is well known, antitoxin can only be detected and measured by its characteristic of neutralizing toxin. The degree of neutralization of the toxin by the antitoxin is determined by the injection of a definite quantity of the mixture into guinea pigs. The testing of the potency of the drawings of the serum from the various horses under treatment is apt to leave a certain proportion of the test animals alive, because of their having received, subcutaneously, toxin which had received an overneutralizing amount of antitoxin. The attempt to use these treated guinea pigs several months later revealed the fact that many of the animals were immune. Investigation proved that this antitoxic immunity did not develop until the lapse of four to six weeks. Babes (1895) was the first to inject, experimentally, diphtheria toxin-antitoxin mixtures and to appreciate that, not only slightly underneutralized diphtheria toxin, but also that which was slightly overneutralized would cause the development of antitoxin in animals. A little later (1896), but independently, I made the same observations. Wernicke (1895) noted that guinea pigs actively immunized by the injection of living bacilli and antitoxin gave birth to immune young, and that antitoxin was present in both the mothers and their offspring for at least eight months. In the winter of 1896, I began to use this knowledge practically in starting the immunization of the horses, which were employed for the production of antitoxins, with much overneutralized toxin.

In 1903, I published results showing that enormous amounts of toxin just neutralized could be safely given. An injection into a horse of 100,000 lethal doses of toxin, which has been just neutralized, usually causes the development of about 60 units of antitoxin per cubic centimeter of serum, while the same toxin neutralized sixfold usually causes the production of about 3 units.

In 1905, Theobold Smith studied the duration of immunity in guinea pigs which had received toxin-antitoxin. He corroborated the earlier work of Wernicke and extended to at least two years the time during which guinea pigs retain immunity. Two years later, he published further studies and discussed the possibility of using toxin-antitoxin in the active immunization of children. Later results of tests by Banzhaf and myself have shown that only about 20 per cent of guinea pigs hold their immunity for two years. The time, however, was not yet ripe and six years elapsed before the first human inoculations were attempted, May 8, 1913, by von Behring in Berlin. Some of the drawbacks and practical difficulties appeared quite formidable.

The fact that the antitoxin would take a number of weeks to develop in those not originally possessing it made it not applicable to persons in immediate danger of infection. Therefore, in the presence of diphtheria, immunizing antitoxin injections would still be necessary in families and institutions. Smith's observations and our own indicated that the immunity would last in animals for not more than about two years. If human beings lost their acquired immunity as rapidly, this would necessitate repeating the injection in children every two years, which would be an almost impossible task to accomplish.

In the absence of any simple test for determining which individuals had natural antitoxin and which did not, we were under the necessity of injecting many unnecessarily if active immunization were to be attempted. The success of the treatment was also difficult to determine.

Practical Application of Diphtheria Toxin-Antitoxin in Man.—Von Behring, on May 8, 1913, reported the early results of the injections of neutralized toxin in a small number of persons. Most of them received one or two doses. Before giving the injections he used no Schick tests or other means of testing whether or not the cases were already immune. He demonstrated by repeated tests on guinea pigs, on bleedings from the tested cases, that there was a quick development of antitoxin in many of those treated; but in others no antitoxin was detected at the time the tests were made. The results were therefore inconclusive. We now know that the retests were made too soon to detect the development of antitoxin in those who had none at the time of the injections. Although von Behring alluded to the toxin-antitoxin mixture as his discovery, what he used was exactly what several of us had described and used in experimental animal immunization during the past eighteen years. His real contribution was the demonstration in a few human beings of the safety of the injections and that a development of antitoxin occurred.

The example of von Behring led Hahn and Sommer shortly afterwards to offer the toxin-antitoxin to the 4,300 children of six villages in the district of Magdeburg, where diphtheria was endemic. Of the 1,097 children injected, 633 received the full series of three injections; 255, two injections and 209, one. The Schick test was not used before or after treatment, so it is impossible to know how many of the injected children possessed natural antitoxin and how many of the others developed it. In the light of our present knowledge it would be fair to assume that at least three-fifths of the cases treated were immune because of the natural antitoxin present and that three-fourths of the remainder became so because of the injections.

There was no difference in the development of cases of diphtheria among the treated and the untreated portion during the first two weeks following the completion of the injections; but after that time there was a lessening of the number in the treated portion. The immunization had no apparent effect on freeing carriers from infection. Until after the War, no further observations or immunizations were made in Europe, and since the War only a few immunizations have been carried out.

Before and during the period of the War, the practical value of the toxin-antitoxin injections was subjected to continuous investigation by workers in the Department of Health of the City of New York. The results obtained and the conclusions drawn are as follows:

Antitoxin Response and Permanence of Immunity Acquired.—Late in 1913 we began the practical use of toxin-antitoxin injections for the immunizing of children against diphtheria and through thousands of injections established the facts that the procedure was harmless and that after three injections about 80 per cent of those individuals possessing no antitoxin, or insufficient antitoxin to protect from diphtheria, developed immunity. Those showing positive Schick reactions, and receiving two injections, developed negative Schick reactions in about 70 per cent; those receiving one injection, in about 50 per cent. We soon realized that the most important problem was the duration of the antitoxic immunity in those that had developed antitoxin. A satisfactory answer to this question required that immunizations be carried out in institutions where the children would be under observation for a number of years. A few suitable institutions were immediately sought for and obtained by Dr. A. Zingher and, later, additional ones were added by Dr. M. C. Schroder. We have thus begun observations on some 10,000 children and have been able to keep them under supervision for from three to seven years. From year to year, Drs. Zingher and Schroder are reapplying the Schick test to these original children. With a few of them we are now beginning the eighth year of observation. We have had no serious immediate or late after effects. In these institutions diphtheria has not developed in any child who has received three injections. Eighty per cent of those who received three inoculations have developed sufficient antitoxin within three months to prevent the positive Schick reaction. Fifty per cent of the remainder developed antitoxic immunity sufficient to give the negative Schick test before the end of the first year. The remainder received then or later a second series of injections and all of these concerning whom we have information became immune. In some later investigations, we have met with occasional children who resisted even two series of injections.

As an illustration of the methods used in retesting the children from year to year in the institutions, Table I is given. In it are entered the results of frequent Schick tests of 28 children who, having been given positive Schick tests, received immunizing injections and later gave negative reactions; these children remained in the institution and continued negative during five years. Of these, 14 remained and continued negative for six years. The following table shows the records of persons originally giving positive Schick reactions on November 16, 1915, and the individual results for five, six and seven years after three toxin-antitoxin injections given on November 20, 25, and December 3, 1915.

TABLE I—RETESTS

Observation Child Number	January 29, 1916	June 29, 1916	January, 1917	January, 1919	January, 1921	January, 1922	January, 1923
1	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—
4	†	—	‡	—	—	—	—
5	—	—	—	—	—	—	—
6	‡	—	—	—	—	—	—
7-12	—	—	—	—	—	—	—
*13	—	‡	—	† *	—	—	†
14	—	—	—	—	—	—	—
15	—	—	—	—	—	—	§
16	—	—	—	—	—	—	
17	—	—	—	—	—	—	
18	†	—	—	—	—	—	
19	‡	—	—	—	—		
*20	‡	—	‡	† *	—		
21	†	—	—	—	—		
22-26	—	—	—	—	—		
27	—	—	‡	—	—		
28	—	—	—	—	—		

*Given an additional series of three injections.
†A very faint Schick reaction.
‡A very moderate Schick reaction.
§Fourteen of the 28 present in 1921 had left.

Discussion of Results of Tests.—Twenty-two became negative within two months, 27 in seven months; 25 of these remained negative during the five years. One of the remaining became finally immune and 2, Numbers 13 and 20, required a second series of injections in 1919.

In cases such as 13 and 20, it is impossible with our present knowledge to determine whether the difference in the degree of reaction is wholly due to a fluctuation in the amount of antitoxin present or whether the deviation from the negative is partly due to a variation in the strength of the toxin used in the Schick retest or to error in the placing of the supposedly intracutaneous injection.

The results in the 28 children are representative of those obtained in the other institutions. With one or two exceptions among hundreds of children, all who did not respond to the first series of injections became negative to the Schick Test after the second treatment. The earliest tests were done by Dr. Zingher, the latter one by Dr. Schroder. Table II gives the results of attempted immunization as shown by the Schick test three or more months after treatment with three injections by toxin-antitoxin. The tests were made by Dr. Schroder from the public schools of Brooklyn.

TABLE II—RESULTS OF ATTEMPTED IMMUNIZATION AS SHOWN BY SCHICK TEST

Number of School	Total Number Children Retested	Positive Cases Which Became Immune	Per Cent	Length of Period between Treatment and Retest
158	370	254	68.7	3 months
156	329	292	88.8	3 months
173	163	144	88.9	4 months
29	57	45	79.0	5 months
142	127	112	88.0	5 months
50	82	74	90.3	6 months
16	241	216	89.7	6 months
72	199	195	98.0	6 months
109	141	99	70.0	6 months
4	103	91	88.4	7 months
Total........	1,812	1,522	83.9	

The knowledge that about 80 per cent of the children who possess no diphtheria antitoxin develop it after three injections of toxin-antitoxin and with very few exceptions retain it for at least six years, and that those who partially fail to respond do respond after a second series of treatments, affords us ground for the belief that we have a practical means of immunizing the child population of the country. Even if our belief that this change in the antitoxin content of these children is a permanent one should prove erroneous, it would merely mean that one would have to repeat the injections at such time as the immunity was found to disappear.

At the same time that Drs. Zingher and Schroder were endeavoring to determine the duration of the antitoxic immunity stimulated by the injections, they also repeated the Schick tests in the children who had given negative reactions originally. It was of extreme importance to determine whether the development of natural antitoxic immunity was a permanent acquisition.

Permanence of Negative Schick Reaction in Persons Who Develop Natural Immunity.—At the Convent of St. Dominick, 90 of the original children who had given Schick negative reactions with Dr. Zingher's tests remained for seven years. These children were retested at the two, five and seven-year periods by Dr. Schroder. In the retests, 83 of these children showed negative reactions, while 7 showed positive reactions in one or the other retest. It is an interesting point as to whether the children who were negative originally had lost their antitoxin or whether the apparent change in reaction was due to other causes. We know from making the double Schick test (that is, one test on each arm) on several hundreds of children, that routine tests made even by an expert are apt to show occasional errors. In this test series we found that about 2 per cent of the children showing positive tests had them only on one arm. There was, therefore, no doubt that in 2 per cent of these children one of the two injections had been inserted too deeply so that the toxin did not remain in the skin and therefore could not produce the reaction. We know also that slight differences in the strength of the toxin solution cause a borderland case to give either a negative or a positive reaction. Differences in technic and in toxin solution possibly account, therefore, for the apparent change in one or all of the four cases. On the other hand, we know that the amount of antitoxin in an individual changes somewhat from time to time, so that it is possible that one or all of the four cases might have reacted at one time and not at another to the standard Schick toxin properly given.

Whatever the explanation of the apparent change in four cases, we have the remarkable fact that nearly 92 per cent of the originally negative children remained absolutely negative during seven years. Practically the same results have been obtained in all the other institutions.

Influence of Age on Susceptibility and the Need of Immunizing Injections.—It is common belief that the mortality from diphtheria is greatest at the ages of one-half year to four years inclusive; that it then drops steadily until at ten years it is quite low and so remains during the rest of life. The figures in Table III give evidence that this belief is founded on fact.

TABLE III—DEATHS FROM DIPHTHERIA GROUPED BY SEX AND AGES, CITY OF NEW YORK, YEAR 1917

Age	Males	Females	Total	Per Cent
Under 1 year	73	60	133	11 +
1 to 4 years incl.	390	319	709	60 +
Total under 5 years	463	379	842	72 +
5 to 9 years incl.	119	132	251	21 +
10 to 14 years incl.	9	13	22	2
15 to 19 years incl.	6	4	10	1
20 to 24 years incl.	2	8	10	1
25 to 60 years incl.	9	14	23	2
Total all ages	608	550	1,158	

The greater liability to infection during the first years of life is clearly shown in the results from the Schick test. Our findings in New York City are as follows:

TABLE IV—AVERAGE SUSCEPTIBILITY OF VARIOUS AGES TO DIPHTHERIA, AS INDICATED BY THE POSITIVE SCHICK DIPHTHERIA-TOXIN SKIN TEST, IN NEW YORK CITY *

	Age	Schick + (Susceptible) Per Cent
Months	Under 3	15
Months	3 to 6	30
Years	½ to 1	60
Years	1 to 2	70
Years	2 to 3	60
Years	3 to 5	40
Years	5 to 10	35
Years	10 to 20	25
Years	20 to 40	18
Years	Over 40	12

* Zingher and others have shown that the percentage of positive Schicks is much higher in those who are living in or have recently come from the country. At the older ages it is more than double the figures given.

Zingher and others attribute this to the greater tendency of the children in crowded communities to become carriers of diphtheria bacilli. He has assembled a considerable amount of evidence to support this view. This is probably an important factor but not the only one. Racial conditions and inheritance probably also play their part.

Immunizing Effect of Toxin-Antitoxin Injections in Infants at Birth and during the First Two Years of Life.—If it were possible to immunize young infants this would be most desirable. In order to test this possibility 2,000 infants were given full doses on the third, eighth and eleventh days after birth. Most careful observations revealed absolutely no deleterious effects. At the end of a year 100 of these infants were retested. Only 52 per cent gave negative Schick reactions. Since untreated infants of this age give about the same result, it is evident that the combined effect of immature cells and the overneutralization of the toxin-antitoxin present (because of the passive immunity derived from the mother) prevents any appreciable response at birth to the toxin-antitoxin injections. Infants aged six months and over gave far better results.

Thus Dr. Blum observed the results of the injections in a number of older infants, in the Home for Hebrew Infants. His figures are given in Table V.

Dr. Byard also reports very favorable results among children in private homes. Many of these were not given the Schick test before receiving the immunizing injections. It is fair to assume that about 50 per cent would have given negative Schick reactions. Of 286 such children, more than half of whom were under one year when injected, he noted the following results: 143 (under one year when injected) when retested after seven months showed 136 negative, 5 positive and 2 very doubtful Schick reactions. Of the whole number 7, or 2.4 per cent, when retested at the end

TABLE V—RESULTS OF TOXIN-ANTITOXIN INJECTIONS IN SCHICK POSITIVE CHILDREN

Number of Infants	Age	Toxin-Antitoxin Injections	Lapsed Period at Time of Retest	Results of Schick Test
6	5 months	3	3-5 months	100% immune
5	5 months	3	9 months	100% immune
3	6 months	3	4 months	100% immune
4	7 months	3	4-5 months	100% immune
12	8 months	3	4-5 months	100% immune
—				
Total 30				

of eight months were definitely positive. Eighteen months after the injections 1.8 per cent were positive. These results are certainly very encouraging.

These results of Blum and Byard among infants aged four months and over are of extreme practical importance because from six months to three years is the period when immunization is most necessary and when it creates the least disturbance.

Constitutional and Local Reactions Following Toxin-Antitoxin Injections.—These are negligible in the infant; slight and infrequent in the young child; moderate or rather severe in perhaps 10 per cent of older children, and slight, moderate or quite severe in a larger percentage of susceptible adults. The effects are due mostly to the protein contents of the culture fluid and are not due to the toxin as such. This is evident because almost the same reaction follows the injection of the toxic broth rendered atoxic by heating, or of a solution containing a minute quantity of autolyzed diphtheria bacilli. If the toxin were the only cause, there would be little or no reaction in immune persons. As is well known some of these show fully as much reaction as those who have no antitoxin. Those individuals who give the strong pseudoreactions with the heated or unheated toxin of the Schick test are those who give the most severe reactions with the toxin-antitoxin injections. However, some who give no pseudoreaction with the Schick test give moderately severe reactions to the toxin-antitoxin injections. The horse serum is present in such a minute amount as to cause no appreciable reaction except in a few extremely susceptible individuals. It does seem to sensitize them appreciably to later doses of horse serum.

In children of school age, with the old preparations about 10 per cent develop fairly sore arms and temperatures of from 99° to 103° F. About 5 per cent feel miserable enough to stay at home from school for one day, and a very few for two days. With the new preparation the reactions are much less. We have given about 500,000 inoculations without a single infection. Children that are constipated are advised to take a laxative on the day of the injection and to apply a moist dressing to the arm if swelling and soreness develop.

In adults, the reactions are about as severe as with the typhoid inoculations. The most severe reactions are restricted almost entirely to those who develop the marked pseudo reaction with the heated or overneutralized toxin. The following history gives an account of one of the most severe reactions that we have encountered:

A nurse, while in another hospital, received the Schick test on December 1. This is reported to have produced a large oval area of redness which persisted with pigmentation and scaling for several weeks. The control test showed a smaller area of redness which faded after a few days, leaving a pigmentation behind. She was considered to have shown a combined positive and pseudoreaction. For this reason on admission as a nurse to the Willard Parker Hospital she was given toxin-antitoxin subcutaneously in the right arm on February 8. In the evening the arm in the region of the injection felt sore and looked red. The next day the soreness and tenderness were more marked. Highest temperature was 103° F. and the patient was confined to her bed. The next day the temperature rose only to 99°. Right arm showed moderate redness of the lower two-thirds, some induration and tenderness, slight axillary tenderness.

Practical Results of Use of Immunizing Injections among Children.—Sufficient time has not elapsed to make a careful estimate of the effects of the immunizing injections. It must be recognized that the recent preventive work against diphtheria has consisted not only of giving the injections but also in spreading information of the use of antitoxin.

It is impossible with these two preventive measures to apportion how much of the improvement belongs to each of them. During the past three years the number of cases in New York City has diminished by 50 per cent and the death-rate has decreased from 20 to 9 per 100,000. In the many institutions under our care no cases of diphtheria have developed among those who showed a negative Schick test or received three immunizing injections. There have been a very few cases in other institutions which have not been under the supervision of the department in which children showing a negative Schick test have developed mild cases of suspected diphtheria. The names of 90,000 of the tested children controlled by 90,000 of the names of the untested children have been filed. All cases occurring among the school children during the winter months (1922-1923) were looked up in this file. It was found that four times as many children developed suspected diphtheria among the control cases as among the tested cases. The disease was also of much greater average severity in the control cases. Among these, 17 cases, whose names were in the file, have been admitted to the diphtheria wards of the Willard Parker Hospital. Fourteen of these were among the control cases and 3 among the tested cases. Not one of these 3 cases in the Schick negative-children showed clinical evidence of undoubted diphtheria and 2 of the cases contained no diphtheria bacilli. Of the control cases, 4 were very severely sick with diphtheria. It is our intention to repeat these observations next winter so as to note whether the same difference continues from year to year.

The following statement divides all the reported cases of suspected diphtheria as they occurred among the 180,000 indexed children during a period of five months. In the cultures from some of these children, diphtheria bacilli were not found.

Cases Reported by Physicians As Clinical Diphtheria

In Brooklyn	
26,000 originally Schick-negative children (observation from Oct. 1 to Feb. 15)	2
15,000 originally Schick-positive children got, as a rule, 3 injections	*4
40,000 untreated control children of same ages	27
In Manhattan	
31,000 Schick-negative children (observation from Oct. 1 to Feb. 15)	4
19,000 Schick-positive children, 3, 2 or 1 injections	7
50,000 untreated control children of the same ages	43
Summary	
57,000 Schick-negative children (observation from Oct. 1 to Feb. 15)	6
33,000 Schick-positive children injected with toxin-antitoxin	11
Among a total of 90,000 Schick-negative or injected children	17
Among a total of 90,000 control children untreated	70

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* One received only 1 injection. One was shown on retest to be positive. A second series of injections was refused.

New Preparation of Toxin-Antitoxin.—Ever since commencing the use of the toxin-antitoxin injections in man, it has been our endeavor to remove as far as possible the annoying protein reactions which follow the immunizing injections. Dr. Banzhaf, who has charge of the chemical side of this study, has up to the present time found it impossible to separate the autolyzed bacillus substance and other proteins from the specific toxin. This failure to purify the toxin led us to test out the correctness of our opinion that a large amount of nearly neutralized toxin was more valuable than a smaller amount of less neutralized toxin. We therefore gathered observations on the results obtained with preparations containing quite different amounts of toxin but always with such additions of antitoxin that 1 c.c. of each of the mixtures had the same toxic effect in guinea pigs. We noticed that these different preparations gave the same immunizing results but that those having the least amount of toxin and therefore least amount of the accompanying bacillus substance showed the least local reactions. We therefore decided to try four fatal doses of toxin (one-tenth of an L + dose of our product, which is about one-thirtieth of the amount in our standard preparation), with the hope of finding that the results would be equally good and the reactions very much less. The results obtained by Schroeder from the different preparations are shown in the two accompanying tables and are very favorable to the new preparation.

TABLE VI—ANTITOXIN DEVELOPMENT PRODUCED BY THREE INJECTIONS OF DIFFERENT MIXTURES

Amount of Original Toxin in 1 c.c. of Mixture	Number of School Children Receiving 3 Injections	Per Cent of Non-immunes Shown to Be Immune on Schick Retest Four Months Later
*1/10 L + (4 lethal doses)	490	90
½ L + (20 lethal doses)	304	95
3 L + (120 lethal doses)	318	92
5 L + (200 lethal doses)	487	85

* The mixture is made by adding three-fourths of a unit of antitoxin to one L + dose of toxin. The toxin and antitoxin should be diluted in cold water and the two solutions mixed immediately. If the toxin is diluted in water at room temperature it deteriorates rapidly.

TABLE VII—COMPARISON OF LOCAL AND CONSTITUTIONAL REACTION TO NEW AND OLD PREPARATION

Reaction	* New Preparation 1/10 L +		Old Preparation 3 to 5 L +	
	Per Cent in Children	Per Cent in Adults	Per Cent in Children	Per Cent in Adults
No local reaction..............	25	26	0	0
Slight local reaction...........	64	50	41	28
Moderate local reaction........	11	19	37	28
Marked local reaction.........	0	5	22	23
Of those showing marked reactions there was a rise of 1° to 3° F. and other constitutional symptoms	0	0	6	20

* If the 1/10 L + preparation is underneutralized more than the amount advised there will be a local reaction from the excess of toxin.

It is impractical to use pure toxin instead of toxin-antitoxin on account of its causing local irritation when used in sufficient amount to be effective.

Owing to these favorable reports we decided to use the new preparation, and it is evident that our example is being generally followed. Because of the fact that the new preparation is a little less stable, it should be used within four months of its release from the laboratory.

The Substitution of Toxoid for Toxin-Antitoxin

Toxoid formed from toxin by the action of 0.1 per cent formalin has given very good results and may even supersede toxin-antitoxin. It has the slight advantage of not causing any sensitization against horse serum.

We believe that the removal of the fear of severe reactions following the injections helps greatly to popularize the use of the toxin-antitoxin.

Relation between Toxicity of Toxin-Antitoxin and the Immunity Response in Guinea Pigs, and between Toxin-Antitoxin and Unmodified Toxin

The final problem we had to solve was the toxicity of the mixture. The results of a long series of tests have led us to the conclusion that, while a mixture neutralized to an extent that 5 or even 10 c.c. are required to produce paralysis in a guinea pig, it will act as a stimulant of the production of antitoxin in children, yet this is less effective and no safer than one somewhat more toxic. The following table shows the results of our last series of tests.

TABLE VIII—TOXICITY OF THE FOUR PREPARATIONS

Most Toxic	Less Toxic	Still Less Toxic	Least Toxic
1 c.c. causes death in 12 to 18 days 5 c.c. causes death in 3 days	1 c.c. causes death in 20 to 22 days 5 c.c. causes death in 5 to 10 days	1 c.c. causes paralysis 5 c.c. causes death in 15 to 18 days	1 c.c. causes no paralysis 3 c.c. causes paralysis 5 c.c. usually causes death after 30 days
Results of Schick Test Eleven Weeks Later			
59 neg., 2 pos., 96 per cent immune	67 neg., 11 pos., 86 per cent immune	25 neg., 9 pos., 73 per cent immune	36 neg., 44 pos., 45 per cent immune

The most toxic preparation caused some excess of local irritation when used in children so that, by choice, we use the second or third preparation. The least toxic is so far inferior in immunizing power that it should not be used if more suitable preparations are available.

The Reasons for Immunizing School Children

We found it very much more difficult and expensive to gain access to the young children than to those of school age. The cost of immunizing one child of preschool age was about seventy-five cents, while for a school child it was but twenty cents. Undoubtedly our main reliance must be on the private physicians for the immunization of the preschool population. The work in the schools, while it affects children who have passed the age of greatest danger, is of the utmost importance. Immunization of school children besides preventing a few deaths and many cases of diphtheria would also, in doing so, prevent to a large extent diphtheria being taken from a school to the home. The consideration by parents of the question of having the child at school immunized prepares their minds to have the younger children done by the family physician. I believe that the time is not far distant when it will be demanded by the majority of parents that their children receive the immunizing injections near the end of their first year. If this becomes a general practice, I believe that diphtheria will become a rare disease.

CHAPTER XXII

WHOOPING-COUGH

JOHN RUHRÄH

REVISED BY GROVER F. POWERS

Synonyms.—Pertussis (Sydenham); tussis convulsia; kink-cough; chin-cough; French, *coqueluche;* German, *Keuchhusten;* Spanish, *tos ferina;* Italian, *pertosse.*

GENERAL CONSIDERATIONS

Definition.—Whooping-cough is a specific infectious disease, characterized by a paroxysmal or spasmodic cough, usually ending in a long sonorous inspiration and often accompanied by vomiting. The medical writers of ancient times did not describe whooping-cough, certainly not with any clearness, but a disease which is so striking in its symptomatology could scarcely have evaded description. The first epidemic of which we have any record was one which occurred in Paris in 1578, and was fully described by de Baillou. The epidemics of cough previously described by various writers had evidently been influenza. The disease spread to other countries, and Thomas Willis, in 1658, mentioned it as occurring in England, and Sydenham, in 1679, gave a good description of it. During the eighteenth century the disease was frequently observed, and the best articles of this period are those of Plaz, in 1727, and Friedrich Hofman, in 1732. During the nineteenth century the disease spread over the remainder of the civilized world, the last countries invaded being New Zealand, in 1847, and Australia, in 1890. At the present time it is endemic in most of the large cities; and epidemics of more or less severity are so frequent as to attract no attention, and not noted except in special statistical articles.

Etiology.—It should be stated that the disease varies in virulence from year to year, and seems to be more severe and also more frequent in cold climates. It is much less severe in weather which permits children to be out of doors, and epidemics are less apt to happen under such conditions, as people are not crowded together, and so infection is less frequent. *Almost everybody is susceptible,* and the majority of persons have the disease some time during their life. Infants under six months of age are less susceptible, but there are instances on record in which symptoms of the disease were observed on the first day, a mother in this case having taken care of a child with whooping-cough. Girls are said to be more susceptible than boys, as are also children whose resistance is lessened by having had other infectious diseases, and children who are below the average standard of health. The disease is most frequently seen between six months and five years of age, and over half the cases occur between six months and two years of age. Susceptibility decreases with age, but it may be seen in adult life and even in old people. It is interesting to note the rule that paroxysms are more severe in nervous children than in others, and Wimmer and Meissner are authority for the statement that children deprived of some of their senses, such as the deaf, dumb, and blind, usually have the disease in a mild form.

Various bacilli have been described as the cause of whooping-cough, but a small bacillus described by Bordet and Gengou is probably the organism which produces it. This organism resembles, more or less, some of those which have been described by other authors, and the difference may be due to the difference in technic. In a general way it may be said that the organism resembles the bacillus of influenza, although it may be easily separated from it by agglutination reactions. This bacillus is present in the bronchial mucus during the first few weeks of the disease, and later on is isolated with difficulty, or not at all. This coincides with the general impression of those who have had much to do with the disease, that it is most infectious during the first two weeks.

The *transmission of the disease* is a matter of considerable importance. It is usually transmitted by direct contact, and but a very short exposure is necessary for infection. In some instances the infection seems to take place in the immediate neighborhood of a case, and in these instances it is quite probable that the infection is caused through the small particles of sputum which are sprayed about the child during coughing. The disease is apparently infectious from the beginning of the first symptoms. The infectiousness is probably most marked during the first two weeks, but occasionally it is transmitted later. Transmission by a third person is rare, and whooping-cough carriers have never been described. The disease is not, as a rule, transmitted by fomites, although this may occur. One of the best examples of this is the case of a woman whose two children had whooping-cough, and were on board a ship which touched at St. Helena. The children of the washerwoman who laundered the children's clothing contracted the disease, there being no other cases of whooping-cough on the island at that time. In hospitals and institutions the disease shows considerable variations in its infectiousness. Where there are a great many children who mingle together closely, or when the beds are too near each other, or when there is overcrowding generally, epidemics are frequent and usually severe. In well-run institutions, where the air space is sufficient and ventilation good, where the beds are far apart and the children kept separated, the danger of infection is greatly lessened; and, if the sputum is carefully looked after, infection may be avoided altogether. This would seem to prove conclusively that the virus causing the disease is not transmitted through the air except as it may be sprayed in the sputum, or be carried on dust.

Recurrences of the disease are quite rare, although they have been noted. It is almost impossible to state definitely the length of the *period of incubation,* but usually from one to two weeks pass from the time of infection to the onset, while sometimes it would seem that only a few days are all that is necessary. If sixteen days pass and the disease has not made its appearance, the chances are that it will not develop. It is well to remember that the *disease is characterized by three stages.* The first, a prodromal stage or stage of invasion, in which the symptoms do not differ materially from an ordinary bronchitis, except perhaps that the tendency to cough at night is more marked, and that there is usually a marked increase of the small mononuclears. This stage lasts from a week to ten days, or sometimes two weeks. The second, usually called the spasmodic or paroxysmal stage, lasts for a number of weeks, and then the disease passes into the third stage, that of decline, which may last a week or two longer.

There are numerous *complications* of whooping-cough. These are due partly to the toxin of the disease and partly to the severe coughing. Among the most important are hemorrhages, which are probably due to a combination of the above. Bronchitis is always present during the prodromal stage, but should be regarded as a complication if it occurs later. Nine-tenths of the deaths are due to bronchopneumonia. Lobar pneumonia is seen more rarely, and is not as fatal. There are numerous disturbances of the nervous system both during the disease and following it, the most important of which is cerebral hemorrhage with its usual sequelæ.

The *misuse of drugs* in the treatment of the disease is a frequent cause of symptoms which may be erroneously attributed to whooping-cough. The most frequent of these are delirium, dry throat, and dilated pupil, from the use of belladonna or atropin; the tinnitus, gastric disturbances, rashes, and other symptoms from quinin; the drowsiness or even unconsciousness from narcotic drugs; the heart failure, cyanosis, and great prostration due to the coal-tar derivatives.

It should also be noted that the other infectious diseases of childhood are liable to affect children with whooping-cough; and, when met with, are particularly severe. It is also important to call attention to the fact that whooping-cough is a disease in which there is a high mortality, notwithstanding the fact that the laity and most physicians seem to regard it as a mild disease. It usually causes more deaths than scarlet fever. The older the child the better the prognosis. Nine-tenths of the deaths are due to pneumonia, and among the other causes of death are: inanition, which is usually caused by loss of sleep and constant vomiting; convulsions; hemorrhage into the brain; external hemorrhage; asphyxia; and syncope. Deaths are more common where hygienic surroundings are bad than among the well-to-do.

PROPHYLAXIS

This is a very important subject and one which is practcially overlooked by most physicians and by the laity. There is, perhaps, no disease causing the same amount of suffering and the same danger to life as whooping-cough in which there is an equally shocking disregard of the rights and feelings of others. Of course the reason is not far to seek, namely, the child is able to go about and instructions are usually given to keep it in the fresh air as much as possible. The spread of the disease can only be prevented by keeping the child away from other children who have not had the disease, and the doing of this lies with the parents of the child. In every instance it is well to explain the reasons for keeping the child away from others, and to insist upon this being done. Particular stress should be laid upon the avoidance of the infection of young children and of those with other diseases. It should also be borne in mind that there are no measures which will prevent the patient from taking the disease if he is susceptible, except keeping away from individuals who have it. The patient is to be regarded as a possible source of infection until the paroxysmal stage of the disease has passed, although the earlier stages of the disease are the ones in which particular care should be exercised. Disinfection (by the use of soap and water, fresh air and *direct sunlight*) of the apartments occupied by a whooping-cough child should invariably be undertaken if the rooms are to be occupied either by infants or by young children, especially those in ill health. Under ordinary circumstances, however, disinfection is scarcely necessary, as the organism causing the disease dies of its own accord after a short exposure to the light and air.

Whooping-cough is reportable in many states but often very little attention is paid to the law. One of the most effective means of preventing the disease seems to be the use of some distinctive arm band or sash for all children having the disease so that they can be out of doors, but at the same time other children and nurses will be warned that the patient is a source of danger. The use of separate waiting rooms in dispensaries or separate hours for the treatment of whooping-cough cases is to be advocated, and special hospital provision should be made for cases that will be isolated satisfactorily.

TREATMENT

It should be borne in mind that, up to the present time, no remedy has been found which will in any way shorten the duration of whooping-cough; and, while this is true, it may also be emphasized that much can be done to render the suffering from the disease less severe, and also prevent many of the complications.

It is too often regarded by both the laity and physicians as a disease for which nothing can be done; and there are many popular sayings which serve to keep this impression alive, the most pertinent of which is perhaps that of the Bavarian peasants, who say that it lasts until it stops. There is another saying attributed to Franck, "You can kill a whooping-cough child before the affection has run its course, you can never cure him," which has perhaps had a good deal to do with the attitude of the profession in regard to the disease. There is scarcely any ailment which has had as many drugs and other measures suggested for its cure as pertussis; and almost every week sees some new remedy suggested, while the number of nostrums claiming to be specific is legion.

Hygienic Measures.—These are of equal if not of greater importance than medication. The first point to be noted is to keep the child in the *fresh air* as much of the time as possible. A *quiet out-of-door life* is the best; but if, owing to other circumstances, such as inclement weather, this is not possible, the apartments occupied by the child should be thoroughly ventilated and the sleeping room thoroughly aired during the day, and an abundance of fresh air supplied during the night. When the child cannot be out of doors, moving from one room to another is of considerable value, the room which the child occupied being thoroughly aired in the meantime. The second point is to have the child lead a quiet existence, as free from excitement as possible, since anything which tends to arouse the child is liable to bring on severe paroxysms of coughing; fits of anger, which, in the irritable condition accompanying whooping-cough, are all too easily excited, should be carefully avoided. The child should be protected from severe weather, and, when out of doors, should be kept out of the wind as far as is practicable, and especially out of the dust and away from irritating vapors. This is sometimes difficult in the case of city children, who should by preference be sent to the parks or open squares. The *clothing* should be changed with the weather, the proper amount being the smallest number of garments that will keep the child comfortably warm. Care should be taken not to burden the child with extra covering either by day or night. The *tempera-*

ture of the apartments occupied by the child should, as far as possible, be kept the same. Sudden exposure to cold may bring on paroxysms, but this is no contra-indication to having the child out of doors in cold weather. If the child's *bed* is in a cold room, it is well to have the sheets warmed before the child is placed in bed, so as to avoid the paroxysm which takes place when the child is placed between cold sheets. While the child should be bathed sufficiently to keep it clean, and in hot weather to keep it comfortable, too much bathing should be avoided. The *psychic treatment* is of considerable value. As far as possible, the child should be taught to restrain any desire to cough, as in some nervous children the number of paroxysms may undoubtedly be influenced in this way. As a rule, the paroxysms come on spontaneously, but it should be borne in mind that, while this is true, they may be easily brought on by a great number of external stimuli. For diagnostic purposes a paroxysm may be excited by pressing the finger or the handle of a spoon over the epiglottis. Sudden fright at times lessens the number of paroxysms, but it may also at other times make them more frequent. Children often start to cough by imitation, so that in institutions where there are a number of whooping-cough children the paroxysms seem to be greater than in the same number of children who are kept apart. Very often a number of children will have a paroxysm brought on apparently by one child starting the cough and the rest feeling impelled to imitate it. Under no circumstances should punishment be used, although there are instances on record in which this has been suggested as a means of treatment. Any measure which will lessen the number of paroxysms should be regarded as of value, as by so doing the danger of complication is considerably lessened. Naegeli has suggested a simple mechanical method for relieving paroxysms of coughing, and, while this is more or less generally known, it is very seldom used. The method consists of grasping the lower jaw and pulling it downward and forward after the manner used by anesthetists. If the patient is an adult or a large child he can do this for himself. At the same time this is being done a very deep inspiration should be taken. If this is carried out when the paroxysm is impending, and most patients feel the paroxysm coming on, it will generally succeed in inhibiting the attack. With very small children who are unable to coöperate by taking a deep inspiration the procedure is not so successful. This is perfectly practicable, but I have found that, as a matter of fact, it is of very little service, since it is only the exceptional nurse who will take the trouble to keep the child under sufficiently close observation to apply this method in time to be of any service.

Another mechanical suggestion, and one of considerable value, is that of Kilmer, of New York, who advocates the use of a tightly fitting *elastic bandage* about the abdomen. This, he claims, will not only lessen the number of paroxysms, but will also lessen the number of times which the child vomits. I cannot state positively that, in average cases, it influences either the number or the severity of the paroxysms, but in cases of unusual severity it sometimes seems to do a great deal of good in this direction. There can be, I think, no doubt as to the value of the bandage in lessening the amount of vomiting, and, while it is not specific in its action, it affords remarkable relief in some of the most troublesome cases which one is called upon to treat. The band also is of some value in lessening the abdominal pain so frequently complained of, due to the frequent attacks of coughing. To be of any service the band must be properly applied. The best method is to use a stockinet band similar to those used under plaster jackets, this being applied to the body from the axilla to the pubis. It is kept from slipping down by the use of shoulder straps. On this, stockinet elastic webbing, similar to that used in making elastic stockings, is so applied that it covers the abdomen. In applying it should be pinned slightly on the stretch and sewed on to keep it from curling. I have found that any heavy resistant cloth, such as good stout muslin, may be used for making the jacket, and that a strip of webbing five inches wide may be used for the front from top to bottom. The jacket should be opened in the back and secured by lacing. This will enable it to be applied very snugly and the elastic webbing makes very firm and, when properly applied, even pressure over the entire abdomen. Sometimes it is necessary to secure the lower part of the jacket in front by pinning it to the other clothing. Unless this jacket is applied so that pressure is firm and uniform it is of very little service.

Numerous suggestions as regards treatment have been made, and one idea is that *vaccination* for smallpox influences the course of whooping-cough. This was noted soon after the introduction of vaccination, and various observers since have called attention to it. I have had no experience with it, but Poschi advocates its use at the beginning of an epidemic (see also Vaccination). He believes that it has some curative value if done during the period of incubation, but none if the initial stage has begun. To be of any service, it appears that the vaccination must be done at this time, and those in whom vaccination has been done a year previously seem to derive no benefit so far as pertussis is concerned. Recent reports, however, are contradictory on the favorable influence of smallpox vaccination upon the course of pertussis. Schroble has suggested the use of warm baths on going to bed. The bath should be at least 99½° F., the child kept in it from ten to fifteen minutes and the head kept cool with cold compresses at the same time.

Disinfection of rooms occupied by the patient is a method which is frequently suggested, and Mohn of Norway claims to have shortened the disease by this method. He used sulphur, but formalin disinfection has been tried, and a very dilute formalin vapor is also advocated as a method of treatment. This method of disinfection is of very questionable value.

Breathing compressed air in especially devised chambers also has its supporters. The breathing of the fumes from the lime employed in purifying illuminating gas was formerly in vogue, its chief use probably consisting in getting the little patients out of doors while making the journey to and from the gas works. The injection of antidiphtheritic serum has been suggested, but it has been suggested in so many diseases in an irrational manner that it deserves no more than passing mention.

Diet.—This is a matter of the *very greatest importance* and, in some instances, of great difficulty. In the milder cases light, nourishing food is all that is required, and no especial restriction except that of indigestible articles is needed. Younger children should be placed either on an exclusive milk diet or a diet composed of milk, cereals, and broths, and the same should be given where vomiting is frequent. It is a very good plan to have the child take as much food as possible during the period of the disease in which there is little vomiting, so that, in case much food is rejected later on, the general condition will not have suffered. In some cases almost every meal is vomited, and it occasionally happens that the child suffers severely from lack of nourishment. Many children have died from starvation; for this there is no excuse. Sometimes the best plan is to give the child skimmed milk, or skimmed lactic milk, with 5 to 10 per cent added carbohydrate at frequent intervals. The amount given at each feeding may be small. If one meal is vomited, a second should be given as soon as the stomach is quiet, and it is a good plan to have the meals taken as soon after a paroxysm as possible, as following an attack there is frequently a period of calm during which the food may find its way into the intestine. Where food is refused or the child becomes feeble, tube feeding should be immediately instituted. In some cases the use of thick cereal feedings and the elimination of liquids at mealtimes will materially reduce the amount of food lost. It is sometimes necessary to use sedatives to lessen the number of paroxysms. It is a very good plan to remember that the irritability of the stomach is often the result of improper medication, hence few or no drugs should be used if the vomiting is severe. Treatment of pertussis must be individualized, but most children have fewer paroxysms when in fresh air day and night regardless of temperature.

Use of Drugs.—Almost every drug in the pharmacopeia and many which are not in it have been suggested. These embrace external applications to be rubbed on the body, the use of inhalations, the use of sprays, of insufflation of powders, and the internal or hypodermic administration of various drugs. In regard to the value of drugs to be applied *externally* on the skin I am extremely skeptical. There are one or two widely sold nostrums applied in this manner which I have seen tested, although against my advice, on a large number of cases. I have never seen the course of the disease influenced at all by their use. It should be borne in mind in this connection, as well as in other forms of medication, that whooping-cough is a self-limited disease, that a drug used in the sixth week will often give gratifying results where the same drug given in the first few weeks would be described as useless. The use of *inhalations* is an idea that has attracted many and has led to the sale of various drugs that are to be vaporized by various methods. I have never been able to satisfy myself that any of these had any value, except where there was a complicating bronchitis. In most cases they do more harm than good by interfering with the use of the proper amount of fresh air. In case of *bronchitis,* just mentioned, inhalations of the steam from limewater or a dram of compound tincture of benzoin to a pint of water, or the same quantity of creosote to a pint of boiling water, may be used with a certain amount of benefit. The inhalations may last from five to ten minutes and be repeated at intervals of two, three, or four hours. Plenty of fresh air should be supplied in the interval. Spraying the nose and throat I do not believe to be of any value in uncomplicated whooping-cough, although where there is coryza or irritation of the mucous membranes of the throat it is of some value in lessening the excessive number of attacks which may be caused by the irritated mucous membranes. The habitat of the pertussis bacillus is apparently in the bronchi, and is not influenced by medication of the upper air passages, and this applies also to the insufflation of powders of various kinds. These measures serve to keep the family of the patient occupied and give them a sense of having done something, but, as far as the patient is concerned, unless there are specific indications, on account of complications, they serve more to excite paroxysms than to lessen them. Bravo and Soltman are very enthusiastic over the use of cyprus oil diluted with alcohol in the proportion of 1 to 5, of which 2 or 3 drams (8 to 12 gm.) are poured over the pillow at night or the underclothing during the day. My experience with this method of treatment has not been great, but in a few cases in which I have tried it it did not seem to have any effect one way or the other. The use of drugs internally, or in exceptional cases hypodermatically, properly done, has been the means of affording great relief to the patient. It is well to bear in mind that there is no one drug which will act equally well in all cases, and what will succeed admirably in one case will have little or no effect in another. It should also be remembered that the continuous use of any one drug may be dangerous on account of its depressing effect, or that it may lose its value in lessening the number of paroxysms due to the body acquiring a tolerance for it. Any drug which causes nausea or vomiting should be immediately discontinued.

The drugs which, from my own personal experience, have proved of greatest value are as follows: Atropin or belladonna and heroin I believe to be of about equal value and come first on the list. Heroin, however, should be used in children only under very urgent circumstances. Antipyrin, either alone or probably better combined with codein sulphate or sodium bromid, I should place second, with the distinct disadvantage that it cannot be continued over very long periods of time without danger of antipyrin or bromid poisoning; its use is not advisable in the case of patients with weak hearts, or impaired kidney function. The method of administering the above-named drugs is important. Heroin is best given in the form of heroin hypochlorid in the form of an elixir, and the dose may vary from gr. 1/100 to 1/24 (gm. 0.00065 to 0.0027). This dose may be given, according to the age of the child and to the effect which it produces, in intervals of from four to six hours. Occasionally the interval may be shortened. In some children it causes drowsiness, but if a very small dose is first chosen and the increase made gradually this may easily be avoided. Heroin, in many instances, will cut the number of paroxysms in half and sometimes stop them almost altogether. In other cases it is of particular use in stopping the vomiting. I have repeatedly seen the vomiting cease under its use to recur when the drug was stopped. When the dose is carefully regulated so as to get the smallest amount which will produce the desired effect, it may be continued over periods covering weeks without any untoward effects. It is a good plan to stop it every week and see whether it can be dispensed with, when it may be resumed if necessary. In every case where it is employed the bowels should be carefully regulated, using mild purgative drugs if necessary. The use of atropin or belladonna is of remarkable value in a certain number of cases, and the latter may be given in the form of a tincture of belladonna in doses of from 1 to 10 minims (0.06 to 0.6 c.c.) four or five times a day. I usually prefer a solution of atropin sulphate in the strength of 1 gr. to 2 oz. (0.065 to 64.00 gm.) of water. Each drop of this approximately represents 1/1000 gr. (0.000065 gm.). My method is to start with one drop of this solution and to increase one drop each dose until flushing results. This comes on fifteen or twenty minutes after the administration of the drug, and when it is noted the dose should be diminished one drop, or, if the flushing still persists, to the dose which is just short of causing it, and this dose may be repeated at intervals of three or four hours. This may be kept up over periods lasting for several weeks, although it is well to stop the drug every week for a day or two and note the effect without it. If necessary, as in the case of heroin, it may be resumed. It should be noted that, as a rule, blonds require less than brunettes, and that it may occasionally cause delirium, mydriasis, and dryness of the throat. This is not liable to happen unless the dose has been too large, or the individual unusually susceptible. Antipyrin may be given in doses of from 1 to 5 gr. (0.0625 to 0.324 gm.) and it may be used with or without codein sulphate, in the doses of gr. 1/60 to ¼ (0.001 to 0.016 gm.) according to the age of the child. For younger children the syrup of orange is a very satisfactory vehicle, while older children may take it in capsules. Codein sulphate alone is often of considerable value. Papaverin hydrochlorid may be given three or four times a day. The dosage may be ⅓ to ½ gr. (0.02 to 0.03 gm.) at ten years of age, and younger children in proportion. Quinin, which was suggested by Binz, has the disadvantage that in young children it is exceedingly liable to cause nausea and vomiting and is difficult of administration. In older children the disagreeable effects attending its use, consisting of tinnitus and deafness, are often complained of. The suggestion has been made to use it in doses of about gr. 1/6 (0.01 gm.) for each month of the child's age and about grs. 1½ (0.1 gm.) for each year of the child's age. This should be given four times a day. Bromoform is of decided value on account of its marked sedative action, but poisoning has resulted so frequently from carelessness in its use that it is perhaps best not administered, except where persons of a reasonable degree of intelligence are intrusted with it. It may be given in doses of from 1 to 5 drops on sugar. Emulsions of it have been suggested, and may be used if thoroughly shaken before the dose is poured out, but the drug, being heavy, tends to separate and fall to the bottom of the bottle and this results in the last few spoonfuls in the bottle containing nearly all of the bromoform. There are numerous cases of poisoning on record from this cause. Cocain hydrochlorid may be of value in certain cases of extreme vomiting. Intramuscular injections of ether have been recommended.

In the treatment of the bronchopneumonia of pertussis, the administration of oxygen is of great value. The gas must not be administered by the useless funnel method, but through a small nasal tube which delivers the oxygen directly into the pharynx. Blood transfusions, repeated several times if necessary, are of the very greatest value to these patients with bronchopneumonia.

The vaccine treatment of whooping-cough has not thus far been attended with success. The literature is encumbered with contradictory reports. The most that can possibly be said for the vaccine treatment is that it may have a slight value in prophylaxis.

CHAPTER XXIII

PLAGUE

Richard P. Strong

Since 1904 plague has become a very cosmopolitan disease, and during the past few years human outbreaks of plague have been observed in the United States, in California, Louisiana, Texas, and Florida, and in Mexico and practically all of the Central and South American republics. It has also been present in eastern and southern Africa; in Asia, it has prevailed particularly in India, Japan, and China, the Strait Settlements, Turkey; and in the large islands such as Java, the Philippine Islands, and Hawaii; and in Australia. In Europe practically all of the Mediterranean seaports have been infected as well as a number of the larger ports of England, France, and Spain. It was, however, something of a surprise to many physicians when the published report of Tessier in 1921 recorded 60 cases of the disease which had developed in Paris and been treated in the Claude Bernard Hospital in that city. During 1922, 29 plague-infested rats were discovered in Paris. Drury and Ball have also reported an isolated case of the disease in the city of Dublin in 1921. In view of these facts the prophylaxis and treatment of plague have recently assumed a more general significance and importance to the physician.

PROPHYLAXIS

Plague may be conveniently classified for the purpose of the discussion of the prophylaxis and treatment of the disease, as bubonic, septicemic, and pneumonic plague, according to whether the lymphatic system, the blood, or the lungs are primarily involved. However, attention must be called to the fact in relation to this classification that, in all cases of primary pneumonic plague, the plague bacilli are present not only in the lungs, but also in the blood, almost from the onset, and that, in almost all cases of bubonic plague terminating fatally, the plague bacilli may be found in the blood shortly before death. In a small percentage of cases of bubonic plague, usually not more than 2 per cent, secondary involvement of the lungs may also occur.

Epidemics of plague are usually bubonic in character and in such epidemics there are always a small number of primary septicemic cases as well as some of secondary plague pneumonia. However, a few severe epidemics have been of the primary pneumonic variety. These severe outbreaks have occurred particularly during colder weather. The prophylaxis in bubonic plague and pneumonic plague is obviously somewhat different since the portal of entry of the two infections is entirely distinct, and pneumonic plague is clinically and epidemiologically a different disease from the bubonic form. In bubonic plague, infection is usually acquired through the skin and adjacent lymphatic glands. Epidemics of bubonic plague are associated with rodent infection, and man acquires infection usually secondarily from the rat through the agency of the rat flea. In more exceptional instances fleas from other infected rodents, as the ground squirrel or mice, may give rise to the infection, or infection may occur occasionally from man to man through the agency of the human flea, or occasionally possibly through Pediculus humanus or Cimex lectularius. Hylkema has recently emphasized the importance of the human flea in connection with the recent European human epidemics. In a small percentage of cases bubonic plague occurs in man from exposure of abraded surfaces of the skin to plague-infected material. Instances of such infection have occurred in barefooted individuals with small wounds of the feet, from walking on floors or stepping on material infected with plague bacilli, or through abrasions of the hands in those who have performed autopsies or handled the bodies of those who have died of plague. Infection in human septicemic plague is acquired through the mucous membranes, particularly of the mouth and throat, and the conjunctivæ. Particles of infected sputum introduced into the eye by coughing have produced human septicemic plague. Secondary plague pneumonia during some epidemics occurs in about 2 per cent of the bubonic cases, the lesions in the lungs being of a metastatic character. These isolated cases of secondary plague pneumonia are not so liable to give rise to large epidemics as are cases of primary pneumonic plague. Thus, in recent outbreaks of this character in California in 1919, there were but 13 cases, while, in the epidemic of primary pneumonic plague in 1910, there were nearly 50,000 deaths. In epidemics of primary pneumonic plague, infection does not occur as in bubonic plague through the agency of infected fleas, but directly from man to man aërially through droplets of infected sputum, as was conclusively shown by Teague and the writer in the Manchurian epidemic. This epidemic has been the only severe one of this disease which has been carefully studied in modern times. In no other infectious disease have such enormous numbers of uniformly highly virulent microörganisms been demonstrated in the droplets of sputum. Primary pneumonic plague was produced experimentally in monkeys by allowing these animals to breathe in an atmosphere infected for a few minutes by spraying a culture of plague bacilli.

These three types of plague infection, bubonic, primary septicemic, and primary pneumonic, may all be easily produced experimentally in guinea pigs or monkeys through the different portals of entry as described above.

From this discussion it is obvious that prophylaxis in bubonic and primary pneumonic plague must vary considerably.

General Prophylaxis of Bubonic Plague.—Plague being primarily an infection of rodents, and transmitted commonly to man from such rodents by infected fleas, prophylaxis in bubonic plague consists primarily in the prevention of contact between man and such infected rodents and fleas, and hence in the general destruction of rats and fleas in regions where plague exists or is likely to exist. Since when rats are reduced in number there is more likelihood that rat fleas will seek the body of man for food, it is well to employ when possible measures that will destroy simultaneously both rats and fleas. The elimination of human fleas in areas where plague infection is present is also very important. The physician must realize that not only the infected rodent but also the human plague patient constitutes a focus of infection, and that hence prophylactic measures against plague must include an early diagnosis and detection of cases of human as well as of rodent plague. For this purpose special bacteriological laboratories which permit of thorough isolation and disinfection should be established and equipped with special cages and apparatus for the study and diagnosis of plague. In places where plague is endemic, it is advisable to collect periodically and make examination of rats, since human plague outbreaks are frequently preceded by rodent infection. These examinations are sometimes of very great importance. Plague rats were found in New Orleans two years before the epidemic of human plague occurred. Our Public Health Service has recommended the examination of 1,000 rats per 10,000 human population as affording reliable evidence of plague infection among rodents of a community. Johns goes so far as to say that the appearance of human plague before the knowledge of the presence of the concomitant epizoötic could reasonably well be made the basis of a charge of criminal neglect of a public trust.

The early detection and diagnosis of human cases of the disease are not only important in prevention but also in regard to treatment. All deaths during an epidemic, no matter from what cause, must be investigated and autopsies should be performed and bacteriological examinations made. Cases of the disease should be isolated and their clothing disinfested of any fleas under proper precautions, and the usual disinfection of their excreta and surroundings exercised. The search for patients by house-to-house inspection is a very important measure, since a large number of plague cases are usually concealed during epidemics by their relatives and friends. Ordinances should of course be passed compelling the report of any suspected case. If infected plague cases are found and the construction of the house permits, there should be a preliminary disinfection with sulphur dioxid or some other substance that may be depended upon to kill rats and fleas, and a search made in the neighborhood for secondary cases both in man and rodents. Contaminated objects in and about houses may be disinfected with 1 : 1,000 bichlorid of mercury, 2½ per cent carbolic acid, 10 per cent formalin, or 1 per cent solution of chlorinated lime. In places where plague is endemic or likely to become epidemic, there should be a special hospital as well as a special diagnostic laboratory. Provision must be made for the isolation of human cases upon their arrival until they have been divested of their clothing and disinfested of any fleas. All of the clothing should be immediately placed in a bag and disinfected in a steam sterilizing chamber. Attendants who handle patients on their arrival, or their infected clothing, should wear gloves and special uniforms designed to prevent the entrance of fleas. High boots are particularly desirable. The hospital itself must be well screened and protected from insects and should be rat-free. Obviously particular attention must be paid to the exclusion of fleas in countries where these insects are common. Fabrics and other objects which become contaminated with the discharges should be thoroughly disinfected by proper methods. Cremation of dead plague bodies should be recommended. Protective inoculation should also be advised, particularly for attendants and persons about the hospitals, and for those who are performing or assisting at autopsies upon plague cases. During bubonic plague epidemics the plague hospital, provided it is free from rats and fleas, presents no particular dangers for attendants.

Rodents and Fleas in Relation to Transmission.—The species of rodents which have been most concerned in the spread of plague in various parts of the world are Mus rattus, Mus decumanus, and Mus norvegicus. In California, Citellus beecheyi, the ground squirrel, and in Manchuria, Arctomys bobac, the tarbagan, have played important rôles in causing infection. In South Africa the gerbil (Tartera lobengulæ) and a multimammate mouse (Rattus coucha) have recently been found infected, and have shown a very heavy mortality over a wide area. In Africa, Leger and Baury, in 1922, stated that the shrew (Crocidura stampflii) played a part in the Dakar epidemic. Bacot has shown, that of 34 varieties of fleas found on rodents, 21 species are probably transmitters of plague, and with 11 of these species experiments demonstrating that they transmit plague infection have been performed. In man the species usually causing infection have been Xenopsylla cheopsis, Ceratophyllus fasciatus and acutus, and Pulex irritans. The flea may remain infective for over a month from the time it has sucked the blood containing plague bacilli. Bacot has demonstrated infection in some instances for as long as forty-seven days. It has been stated that epidemics among human beings are not likely to occur unless approximately 0.2 per cent of the rodents are infected, but sometimes a much higher percentage of infection of rodents does not produce a human outbreak even in an insanitary district.

Fumigation for Rodents and Fleas.—In the case of the occurrence of plague on board ship, or the arrival of a ship from a plague-infected port, fumigation of the ship should be practiced. Grubbs also emphasizes the importance of the fumigation of cargo in lighters in plague-infected ports. Hydrocyanic acid gas is undoubtedly the most efficient destroyer of both rats and fleas, but it is very dangerous and a number of fatalities have been reported in connection with its use. The gas developed from ½ ounce of KCN to a space of 100 cubic feet, acting for 4 hours, has generally been regarded as efficient for disinfection. Stitt points out that the great danger from the use of this gas in holds of ships is that it tends to collect in detached spaces or pockets and remains after ventilation of the hold, so that persons entering such spaces suffer the poisonous effects of the gas. While sulphur dioxid is less efficient, it is on the whole the best suited for general use in plague fumigation. Two pounds of roll sulphur for each 1,000 cubic feet of space is regarded as sufficient. The Clayton Gas Apparatus in which the sulphur dioxid is under pressure gives the best results in sulphur fumigation. Carbon monoxid and carbon dioxid and flue or funnel gases from steamers have been recommended for plague prevention work, but they are not so satisfactory, for, while they will kill rats, the fleas are often not destroyed and escape. After disinfection of houses or rooms several guinea pigs may be placed in them for a few days before human occupation is allowed. If many infected fleas are still present, the animals will often contract the disease. The guinea pig may be successfully infected with a single virulent plague microörganism.

Campaign against Rats.—In regions where plague exists an extensive campaign must be undertaken against rats, and traps and poisons should be freely distributed so far as possible, and all buildings which are constructed so as to permit of the abode of rats should be gradually rebuilt in the infected districts. The U. S. Public Health Reports for 1920 give full information regarding rat-proofing in this country. The sewerage should be improved and all filth burned. The separation of the rat from his food supply, and the prevention of his entry into human habitation by rat-proofing through the use of concrete, screening with wire netting, and by other barriers, and by the use of traps and poisons, are all important. The most satisfactory trap is a wire spring or snap trap. This type has been shown to be much more efficient than the wire cage trap. All the rats caught should be sent to the bacteriological laboratory, where they should be examined and records kept concerning the location where the rat was caught. For the detection of plague-infected rats during an epidemic the plan carried out by Heiser of Manila, and which proved effective, was as follows:

> "A list of places in which the plague-infected rats were found was made. Each was regarded as a center of infection. Radiating lines, usually five in number, were prolonged from this center, evenly placed like the spokes of a wheel. Rats were caught along these lines and examined. Plague rats were seldom found more than a few blocks away. The furthermost points at which the infected rats were found were then connected with lines on a map. The area enclosed by these lines was regarded as a section of infection. The entire rat-catching force was then concentrated along the border of the infected section. They then commenced to move toward the center, catching the rats as they closed in. Behind them rat-proofing was carried out. One section after another was treated in this way, until they had all been wiped out."

With reference to rat poisons it is important to call attention to the fact that rats will often not eat bread and food which has been particularly handled by human beings, and therefore the people who handle or cut the bread or food before dipping it into the rat poison should either wear gloves or have their hands smeared with oil of aniseed or some other similar substance, and the board on which the food is cut should be treated in this manner. A very effective poison against rats consists of a phosphorus paste into which the food is dipped. The phosphorus is mixed with glucose in the proportion of 1 to 4, and a fatty base such as lard is employed to prevent spontaneous combustion. Barium carbonate constitutes a very efficient rat poison and a relatively safe one in regard to children and domestic animals. One pound of barium carbonate is mixed thoroughly with 3 pounds of flour or other ground grain in an enamel basin. Sufficient water is added to make the whole into a fairly firm paste. The resulting mass is sufficient for some 2,300 baits, each containing 3 grains of barium carbonate. The baits should be fairly fresh as a stale one is very rarely eaten by a rat.

A number of viruses have been recommended for the wholesale destruction of rodents. These are usually either cultures of the B. typhi murium type or the paratyphoid β type, which is frequently the cause of meat poisoning in man, or of the B. enteritidis or Gärtner type which has been associated with gastro-intestinal disturbances; the so-called Danysz virus, usually B. typhi murium, is pathogenic usually for rats under laboratory conditions, but has feeble powers of propagating itself from rat to rat under natural conditions. It rapidly loses virulence when exposed to light and air. The use of these viruses is not recommended for the general destruction of rats, since they have usually proved to be inefficient for this purpose, and moreover they are not absolutely harmless to man, and instances of sickness and death in human beings from infection by them have been reported. Recent instances of this nature have been reported by Willfuhr, Wendtlandt, Raebiger, and Bahr.

Kunhardt has shown that the economic loss in India due to the rats amounts approximately to 828,000,000 pounds in the past twenty years. This includes losses from disease and mortality, 402,000,000 pounds, and the destruction of grain, etc., by rats, and the cost of rat destruction through antiplague measures. Excellent articles on the subject of rat repression and destruction have recently been published by Dewberry, Jennison, and Murphy. In the case of ships which have touched ports where plague is present, precautions against the transfer of rats from ships to land, or from the ships to lighters, and the docks to ships, when vessels are in port, are very essential. All boats should be kept at least four feet away from the docks and all hawsers should be provided with rat guards. The rat-guarding of ships is a matter of very considerable importance. Rucker has recently described an extremely efficient and practical rat-guard for ships' lines, which is made of galvanized iron. This guard will fit on all lines accurately and it has straps which hold it perpendicular to the line. It is also inexpensive.

Care must be also taken to see that no cases of plague land from ships, and particularly that mild cases, such as those of pestis minor, are not overlooked. Passengers and crews from plague-infected ports should be carefully inspected. The temperature of each person should be taken and it is desirable to make special examination for buboes. If a case of suspected pneumonic plague should be found it should at once be isolated in the hospital and the individuals in contact with it should also be isolated in separate compartments. The employment of immune serum for the contacts should be considered. If a case of bubonic plague is discovered it should also be taken to the hospital, but individual isolation is not so necessary for other passengers. It is advisable for vessels which are constantly trading with plague-infected ports to have the crew given prophylactic inoculation against plague. The period of detention of the personnel for a plague-infected ship has varied from seven to ten days.

Personal Prophylaxis in Bubonic Plague.—This depends upon avoiding plague-infected districts, contact with plague patients, and protection from fleas. People who live under hygienic conditions rarely contract bubonic plague. Manson-Bahr emphasizes the fact that nurses and other attendants on the sick ought carefully to seal up and cover any wounds about the hands, no matter how trifling. The excreta and bed linen of the patient must be carefully handled and sterilized. For those who are compelled to enter and work in plague-infected districts, special precaution must be taken against fleas. High boots with the openings at the top around trousers, closed by elastic or adhesive strapping, are advisable.

Fleaproof suits are also recommended. The use of insecticides such as kerosene or crude naphthalene are sometimes of service in repelling fleas. Prophylactic inoculation has also been advised during epidemics of bubonic plague. As soon as definite symptoms of plague appear in those who have been exposed to infection, plague immune serum should be injected. These subjects are considered in detail later in the article.

Pneumonic Plague.—Every case of primary pneumonic plague constitutes a very dangerous focus of infection. The fully virulent microorganisms are present in enormous numbers in the sputum, often in almost pure culture, and the plague bacilli are also expelled in large numbers into the surrounding atmosphere by coughing. Plague bacilli are not killed by freezing for long periods of time, and hence epidemics of pneumonic plague are particularly serious during cold weather. In order to prevent the spread of pneumonic plague, the cases must be recognized early and rigidly isolated. Suspected cases should also be isolated. There must be separate hospitals for plague patients, for suspect cases, and for contacts. Sanitary cordons should be established against infected areas and there should be strict medical inspection and quarantine for five days. Buildings such as schools, churches, theaters, factories, and markets should be closed. The pneumonic plague hospital must be built so as to admit of individual isolation. No patient should be transferred from the suspect hospital to the plague hospital until a positive diagnosis of plague has been made. The pneumonic plague hospital for suspected cases must also admit of individual isolation of patients. Houses in which pneumonic plague cases occur should be thoroughly disinfected in the manner described for bubonic plague. The excretions and particularly the sputum must be thoroughly and carefully sterilized. All soiled linen must also be disinfected, and walls and floors should be mopped with 1:1000 bichlorid solution. It has been advised that the sanitary staff be inoculated with plague vaccine. However, they should not rely upon such protective inoculation. Teague and the writer found in extensive experiments with monkeys that only about 10 per cent of the vaccinated animals were protected against plague infection by inhalation. The remaining 90 per cent of the animals died of pneumonic plague. Wasilewski, in the epidemic of pneumonic plague in eastern Siberia in 1921, also concluded that antiplague vaccination has no favorable influence in pulmonary plague. For the passive immunization in a household of individuals that have been exposed to infection the injection of 50 c.c. of plague immune serum may be employed. Doctors, nurses, and attendants should be provided with face masks made of eight layers of gauze or four of cheesecloth, which should always be worn when at work in the vicinity of pneumonic plague cases. Goggles also should be worn in examining cases, and gloves when autopsies are performed. A cotton gown should be worn in the wards, and removed on leaving them. Attendants are advised not to shave immediately before entering the wards to attend patients, on account of the danger of infection through the slight abrasions on the face.

TREATMENT

VACCINE THERAPY

While vaccination against bubonic plague as a prophylactic measure has been extensively employed with results warranting its use, no practical application has been made of vaccine treatment in plague. The course of the disease is too acute for such a measure to yield satisfactory results, since the majority of cases die in from three to five days after the onset of symptoms. The treatment of plague may be divided into symptomatic and serum treatment.

SERUM THERAPY

Specific Immunizing Properties of the Serum.—In order to have a proper understanding of the serum treatment of plague and of its value it is necessary to be familiar with the action which the plague immune serum exerts upon the plague bacillus in the animal body, and the manner in which it destroys it. The mechanism by which the plague bacillus is rendered innocuous by such a serum is quite different from that by which, for example, the cholera organism is destroyed by cholera immune serum or the toxin of the diphtheria bacillus acted upon by antitoxic diphtheria serum.

Bactericidal Reaction.—Early investigations seemed to suggest that the plague immune serum exerted a bactericidal effect. Pfeiffer and Dieudonné, of the German Plague Commission, concluded that in plague immune sera specific bactericidal antibodies were present, the action of which was fully analogous to that of the protective substances which had been demonstrated to exist in cholera and typhoid immune sera. Apparently no experiments were made which demonstrated that the plague serum possessed a bactericidal action, although some experiments were performed which demonstrated its preventive action against infection and its curative value. For a time the opinion that plague immune serum exerted a bactericidal action against the plague bacillus became generally accepted, although but little experimental work was carried on upon the subject. Kolle and Martini performed experiments with guinea pigs and rats, in which the animals were inoculated with from 1 to 2 c.c. of plague immune serum and twenty-four hours later were inoculated intraperitoneally with from two to three loops of plague cultures of moderate virulence, suspended in saline solution. Upon microscopical examination of drops of the exudate from the abdominal cavity three or four hours after the inoculation of the bacteria, the majority of the bacilli were found to be swollen, degenerated, and broken up. Rats which had been previously actively immunized against plague by repeated subcutaneous injections of plague cultures, when inoculated intraperitoneally with plague strains of moderate virulence, also exhibited the same bactericidal action toward the bacteria. No antitoxic action could be observed. Markl found that the method of destruction of plague bacilli varied according to the virulence of the organism. When a culture of very great virulence was inoculated into the abdominal cavity of a guinea pig which had been treated with an immune serum after thirty minutes a very extensive leukocytosis occurred, and the bacteria were taken up by the phagocytes. Those bacteria which remained free became agglutinated and grouped about the leukocytes. The control animals without serum died after one to two days, while those inoculated with immune serum lived for from five to seven days.

Anti-infectious or Antibacterial and Opsonic Action.—Later more complete and carefully controlled experiments performed by Kolle and the writer showed that the plague immune serum exerts no other demonstrable and typical bactericidal reaction against the virulent plague organism during the course of an infection than a normal serum. The method of action of plague, cholera, and typhoid immune sera was compared, the bactericidal action being tested in vitro after the method of Neisser and Wechsberg. In spite of many variations in the experiments and in the use of many different sera from different species of animals to supply the complement for the action of the amboceptors, plague bacilli after treatment with the plague immune serum developed as plentifully in the culture media as they did in those instances in which they were treated with normal sera.

In studying the bactericidal action of plague immune serum, the writer experimented with both inactivated serum, to which fresh serum was added to supply the complement, and plague immune serum perfectly fresh and not inactivated. When perfectly fresh sera are employed in these tests it is true that both the normal serum and the plague immune serum exert a lytic effect upon the plague organism; this action appears to depend upon the presence of fresh complement, as it can be abolished by heating the serum previously at 55° C. for one-half hour. It, however, does not interfere in estimating the bactericidal effect of plague immune serum as compared with that of normal serum. A plague immune serum from the horse, not inactivated, which at the time of the experiment in doses of 1 c.c. was able to protect about 90 per cent of the rats inoculated with it against fatal plague infection, was mixed with perfectly fresh rat serum, and its bactericidal value tested according to the usual method in vitro. In order that the phenomenon of the deflection of the complement by amboceptors might not interfere with the reaction the experiments were also performed with varying amounts of the immune horse serum and fresh rat serum. However, again no differences could be detected between the results obtained with these experiments and with those performed in the same manner with normal horse serum to which fresh rat serum had been added.

These experiments appear to demonstrate that the plague immune serum, which is known to possess immunizing power in the animal and which prevents the further development of the infection, possesses in vitro no bactericidal action whatever, that is, similar to that exerted, for example, by typhoid immune serum. It is also clear that the plague bacilli are not only not killed by the immune serum in vitro, but that they remain alive and are capable of subsequent development. Therefore, some other factor must play an important rôle in the ultimate destruction of the inoculated bacilli in the body of an animal passively immunized by the injection of such a serum, and, since the serum alone in the test tube apparently exerts no marked injurious action upon the plague bacilli, it appears that the phagocyte is the additional factor which is necessary to render harmless and to destroy the organism in question.

In elucidating this question it is advisable to consider not only what action the serum has upon the life of the plague organism, but also what action the organism has upon the immune serum. We know that when the specific substances of a serum such as antitoxin or bacteriolysin are brought into contact in vitro with the homologous bacterial antigen a union occurs between them. Although the union between these two substances follows a different law, it is possible to show that such a binding actually does take place, and that the antitoxic serum loses in value after combination with toxin and the bactericidal one diminishes in its specific effect after treatment with the corresponding bacterium. In order to understand this relationship between the plague bacillus and its corresponding immune serum, a plague immune serum was first carefully tested for its immunizing power on rats, and the amount determined which would protect about 90 per cent of the animals inoculated with it against the subsequent injection of a lethal dose of plague bacilli. Fifteen c.c. of this plague serum was then mixed with the living bacteria obtained from fifteen 48-hour agar slant cultures of a virulent plague organism. The mixture was placed in the incubator for two hours at 37° C. Carbolic acid to 0.5 per cent was then added to the mixture which was next heated for two hours at 46° C. and finally thoroughly centrifuged. The clear fluid above was then drawn off from the sediment of bacteria. After the sterility of the serum had been demonstrated its immunizing value was now for a second time tested on rats, and it was then found that the serum no longer protected these animals in the same amounts as it did previous to its treatment with the bacteria, 70 per cent of the rats inoculated with the same dose succumbing when subsequently infected with plague. From this experiment it is clear that a binding of at least a portion of the amboceptors of the plague immune serum to the receptors of the plague bacillus had occurred, and, although the bacteria in question were not killed by the serum, nevertheless a reaction in vitro between the serum and the organism had occurred.

For the further study of the action of plague immune serum other experiments were performed in vivo in the abdominal cavities of guinea pigs. Upon injecting a virulent plague organism into the peritoneal cavity of a guinea pig temporarily immunized by the injection of plague immune serum it was found that Pfeiffer's phenomenon, as observed in the case of the cholera organism in the cholera-immune animal, did not occur, the virulent organism in question did not undergo dissolution, and only when very avirulent strains of plague were employed did the organisms finally become swollen or disintegrated. This latter observation explains the previous results obtained upon this subject. It is true that shortly after the inoculation of the virulent plague strain in the immunized animal a disappearance of the bacteria from the abdominal cavity usually occurs, and that also at first but few animal cells are encountered in the abdominal exudate. Upon investigating the fate of the bacteria by killing animals at different periods of time after the inoculation it was found that shortly after the injection, both in the case of animals immunized against plague and in that of normal animals, the bacteria had been carried to, or made their way to, the cells of the cavity, and particularly to the omentum, to the surface of which they had become adherent. Here many of them were taken up by the phagocytic cells. After a short period the leukocytes became more abundant in the abdominal exudate and many of them were seen to contain bacteria. In many cases in the immunized animal the leukocytes seemed to possess positive chemotaxis for the bacteria, judging from the manner in which the latter were grouped about them. In the case of non-immune animals the plague bacilli outside of the cells increase in number up to the time of the death of the animal. The majority of the bacteria that are found to exist free in the cavity after the short period of their disappearance are short, bipolar, staining bacilli which often seem to possess capsules. A small number of large bacilli, frequently showing involution forms, are also encountered. After the temporary disappearance of the bacteria in the case of the immunized animal, the leukocytes usually become much more numerous in the abdominal cavity.

The phagocytosis of the bacteria continues both by the cells in the omentum and by those free in the abdominal cavity until very few free bacilli remain. However, in the non-immune animals the bipolar staining organisms, which increase up to the time of the death of the guinea pig, do not appear to be taken up by the leukocytes. It would appear that the phagocyte usually ingests only the organisms which have previously been affected by the immune serum.

From what has been said it is obvious that when plague immune serum is brought into contact with the plague bacillus in the test tube the amboceptors of the serum unite with the receptors of the organism and that in the body of the animal the process of destruction is carried on further by the leukocytes which engulf the bacteria which have been so acted upon. It is also evident that the bacteria are not killed in the test tube by the immune serum alone. It appears that, after the bacillus has been prepared for the action of the leukocyte by the immune serum, the latter plays a part in the digestion and ultimate destruction of the organism. This destruction, however, does not always, at least, seem to occur immediately, since, when loops of the abdominal exudate which contain phagocytes enclosing plague bacteria are transplanted to the surface of agar, the organisms under these circumstances sometimes increase within the cells and in some instances burst the leukocyte and partially escape from it.

The destruction of the plague bacillus is therefore effected by the immune animal in a manner partly in accord with the humoral theory of Buchner, and partly in accord with the phagocytic one of Metchnikoff. The action of the serum in its protective effect upon the animal is neither antitoxic nor bactericidal, but may be termed anti-infectious or antibacterial, that is, it is a serum possessed with the power of preventing infection and, from the rôle already described which the phagocytes play in the process, its action may also be said to be opsonic in nature. It also has been demonstrated that the opsonic index of a plague immune serum is higher than that of a normal serum.

Rowland in studying recently the action of plague immune serum arrives at practically the same conclusions which have been just stated, and believes that the essential factor in plague immunity is one which affects the multiplication of the bacillus. In his experiments he was able to show that in the immune animal the multiplication of the inoculated plague bacilli is much less than in the case of the normal animal. In the abdominal cavity of the guinea pig the bacteria were observed inextricably entangled in a mass of fibrin and cells. Many of the cells were filled to bursting point with the bacteria. The fate of the animal seemed to depend upon the rate of the engulfing of the microörganisms by the cells within a mass of fibrin, and the rate of multiplication of the bacteria. If the rate of the engulfing competes successfully with the rate of multiplication, then the animal survives. If, on the other hand, the rate of multiplication of the bacilli is greater than the mechanism of engulfing, phagocytosis, and lysis can compete with, then the animal succumbs to plague. In the immune animal he found there were finally no free bacilli. In the normal and immune animals the difference in the reaction seemed to depend more upon the quantity of bacilli present than on anything else. The number of bacilli in the case of the immune animal was at any stage of the process much less than the number at the same stage in the case of the non-immune animal. In the subcutaneous inoculation of immune and non-immune animals he also came to the same conclusion, namely, that the essential factor in plague immunity is one which affects the multiplication of the bacillus.

Result of Treatment in Animals.—Bearing these phenomena in mind in relation to the mechanism of the action of plague immune serum, it is not difficult to interpret the results which are obtained in the serum treatment of animals experimentally infected with plague, and we find that the success of the serum treatment appears to depend particularly upon the number of plague bacilli in the animal organism at the time of the inoculation of the serum, that is, upon the length of time the serum is injected after the infection has occurred. If the organism is already overwhelmed with bacteria at the time of the introduction of the serum, almost no favorable change will be noted in the course of the disease, because the serum is merely anti-infectious and is not antitoxic.

Thus, of a series of rats inoculated by the writer with immune serum at the time of their infection with plague bacilli, 60 per cent survived and 40 per cent succumbed to the infection; while of another series which were inoculated with the serum twenty-four hours after the plague infection only 40 per cent survived and 60 per cent died. In another series of experiments in which larger doses of serum were employed, and a less severe method of infection, the animals were inoculated with the serum in three series; one at the time of the infection, a second twenty-four hours following the infection, and a third forty-eight hours after the infection. The mortality in the first series was 10 per cent; in the second 40 per cent; and in the third 66.6 per cent. Similar results have been obtained with monkeys, and sometimes it is possible to save those animals which have previously been infected with plague by the inoculation of plague immune serum injected as late as from twelve to twenty-four hours after the time of the infection, provided large doses of the serum are used. With rats it has been shown that if large doses of the serum are used, even animals in which the disease is fairly well advanced may sometimes be saved by the serum.

Result of Treatment in Man.—Turning our attention to the treatment of human cases of plague with serum, we find somewhat similar results. Choksy, who has had a very extensive experience with the serum treatment of plague, states that much depends upon the early and free use of the serum. In patients treated on the first day or within a few hours of the onset of the symptoms one injection of 100 c.c., followed by another after six to eight hours, and then, if necessary, by a third after a similar interval, would cut short the attack if the case were not pneumonic, malignant, or septicemic. He also emphasizes the fact that the earlier the serum is used the more efficacious it is, and that, if good results are to be obtained from serum therapy, the patient must be treated on the first day of the illness. He admits that the serum cannot favorably influence all types of plague, or even the malignant forms of the bubonic type, but he shows that it is the only treatment capable of saving a large proportion in a certain class of patients.

In his last publication regarding the subject he summarizes observations regarding 1,081 cases. There were eliminated from the observations septicemic, pneumonic, and moribund cases, as well as convalescent and semiconvalescent cases, and also those in whom the illness had already lasted for six days or more. The observations were thus restricted to the most acute cases within the first five days of the illness. Every alternate case was then treated with serum. Four hundred cases under the observation of the author were treated in this way. In the serum cases the mortality was 63.5 per cent, and in the 200 controls the mortality was 74 per cent. There was thus a difference of 10.5 per cent in favor of the serum cases. In a previous series of 238 cases treated with the serum, the mortality rate was 59.2 per cent.

By comparing the time of death after admission between the serum and the control cases, it was found that, whereas 79 per cent of all deaths among controls occurred within four days after admission, the proportion was 58.2 per cent among the serum cases, a difference of nearly 21 per cent, the serum having considerably prolonged life. Of 243 cases treated in private practice with the serum, the mortality was as low as 40.7 per cent.

Out of the entire 1,081 patients subjected to the serum treatment 537 died and 544 recovered, the mortality rate being 49.6 per cent; 613 of the cases were treated in hospitals in which the case mortality was 57 per cent, and 468 were private cases in which the mortality was 39.9 per cent. A very striking feature is the difference in the mortality rate according to the stage of the disease at which the serum was injected. Of 316 patients treated on the first day 220 recovered, the mortality being 30.3 per cent. On the second day of illness 300 cases were treated, 142 recovering, or a mortality of 52.6 per cent. The table on page 523 also shows the increased mortality in the cases treated later than the second day of the disease.

The general mortality of plague at that time in India was estimated at 89.9 per cent. The author concludes his observations by stating that the success of the treatment lies in applying the serum very early. Among patients subjected to the treatment within the first few or even twenty-four hours it is noticed that the whole course of the disease becomes altered. The normal duration of the disease from about eight to ten days is reduced to four or five days. Serious complications of the nervous, circulatory, and other systems are averted. The buboes become absorbed,

INCREASED MORTALITY IN CASES TREATED AFTER SECOND DAY OF DISEASE

Duration of Illness	Number	Recovered	Case Mortality Per Cent
First day	316	220	30.3
Second day	300	142	52.6
Third day	246	91	63.0
Fourth day	105	45	57.1
Fifth day	52	20	61.5
Sixth day	14	6	57.1
Seventh day	4	0	100.0

and convalescence is more rapid. After forty-eight hours the serum does not appear to influence the course of the disease perceptibly.

Simpson, in his *Treatise on Plague,* summarizes his remarks in regard to treatment with the statement that, if the serum is injected intravenously and early, it appears to give the patient a better chance of recovery than any pharmacopeial drug, and in some instances the state of the patient after the injection is so much improved that it can only be attributed to the action of the serum.

Kitasato states that the good results obtained from the serum treatment admit of no dispute, provided sufficient quantities are used, 200 to 400 c.c., and that, although we are not in a position to ascribe to the pest serum a value as absolute as to the diphtheria serum, there is no doubt of the efficacy of the former remedy. A series of experiments was conducted by him in Formosa with a view to comparing the results of the serum with those of an early extirpation of the buboes and general systematic treatment. Of the 56 patients treated by the latter method 35 (62.5 per cent) died of plague; while out of the same number inoculated with serum the death-rate was only 33.9 per cent.

Burnett in his report of plague in Queensland has also obtained favorable results in the serum treatment of plague. From 1900 to 1907, 300 cases were observed. The mortality in the cases treated with serum was 29.7 per cent, and the mortality of those who received no serum was 73.9 per cent, as may be seen from the table on page 524.

D'Hostalrich has also recently reported upon serum treatment of plague in Annam. Of 232 cases under the care of this author 21 were treated symptomatically, only 6 of whom recovered, a mortality of 97.5 per cent. Of 190 patients who received daily subcutaneous injections of 40 to 80 c.c. of Yersin's antiplague serum 128 died, or a mortality of 67.7 per cent. In 16 patients who were suffering from very severe infection large doses of serum up to 100 c.c. were injected intravenously; 4 of these survived. In 5 very severe cases intravenous injections of saline solution and serum in large amounts were given; 3 of these recovered. Of 9 serious cases in which the serum was given within the first forty-

RESULTS OF SERUM TREATMENT OF PLAGUE

Year	Entire Number of Cases	Fatal Cases	Mortality—Per Cent	Treated with Serum: Number	Treated with Serum: Fatal Cases	Treated with Serum: Mortality—Per Cent	Treated without Serum: Number	Treated without Serum: Fatal Cases	Treated without Serum: Mortality—Per Cent	Difference in Favor of Serum Therapy
1900	56	25	44.6	..	..	...	..	..	...	...
1901	36	12	33.3	28	6	21.4	8	6	75.0	53.6
1902	82	26	31.7	69	15	21.7	13	11	84.6	69.2
1903	21	11	52.3	16	7	43.7	5	4	80.0	36.3
1904	30	8	26.6	25	6	24.0	5	2	40.0	16.0
1905	28	15	53.5	21	10	47.6	7	5	71.4	23.8
1906	11	7	63.3	7	4	57.0	4	3	75.0	18.0
1907	36	14	39.0	32	11	34.0	4	3	75.0	40.6
	300	118	39.3	198	59	29.7	46	34	73.9	44.2

eight hours of the illness 4 recovered. The author believes the serum exerts a beneficial effect if its administration is begun soon after the onset of the disease. If it is delayed to the third day or later, no favorable results are usually obtained.

In 1913 the British Commission published the results of a further study upon a large number of cases in India, in which the serum treatment was employed. In all 444 cases were observed, 222 being treated with serum and the remaining number serving as controls. Every alternate case in the hospital received serum, the moribund and those who had almost recovered alone being excluded from consideration. A few cubic centimeters of blood were aseptically taken from a vein of each selected case. One-fourth of a cubic centimeter was spread over the surface of an agar tube, and after incubation for forty-eight hours the cultures were examined. The cases were thus divided into four groups. In the first group the cases with no septicemia were classified, and the remaining cases were placed in the second, third, and fourth groups, according to the degree of septicemia present at the time. Two kinds of serum were used: first, the ordinary Yersin serum, prepared at the Lister Institute, London, by the injection of dead and afterward living bacilli; second, a serum prepared from horses injected with a toxic nucleoprotein which it is stated was efficacious in protecting rats from the injection of living broth cultures of plague bacilli. The amount of serum which gave such protection is not stated, nor is the anti-infectious power of the Yersin serum given. The serum was given in large doses, generally both intravenously and subcutaneously. Sometimes it was given subcutaneously only, and in a few cases intravenously only. In many cases further doses were given, usually subcutaneously on succeeding days. The majority of the patients received over 100 c.c. intravenously and some of the patients received altogether 500 c.c. of serum, both by subcutaneous and intravenous injections. Grouping all of the cases together, those with well-marked septicemia, as well as those with no septicemia, at the time of beginning the treatment, it was found that the mortality in the treated cases was 66.2 per cent, and in the cases untreated with serum 73.9 per cent. One hundred and forty-seven of the cases treated with serum died, and 164 of the controls without serum died; 17 of the cases being saved by the serum.

The Commission conclude from their inquiry that it appears that the administration of the available sera is not a practicable means of bringing about any material diminution in the mortality of plague in India. This conclusion seems justified from the statistics which they have compiled after consideration of both the septicemic and non-septicemic cases together, and for the sera employed. The necessity of giving the serum early in the disease if any beneficial effect is to be expected has already been emphasized in this article, and in regard to this point the Commission add to their conclusion the statement that it may well be that better results would be obtained if the treatment could be commenced within a few hours of the onset of the disease. When one analyzes the statistics obtained by them it may be seen, however, that the results are not so divergent from those which have been obtained by some other observers.

In the cases with no septicemia, Group I, there were 70 control cases, 24 of whom died, or 34 per cent; while of 85 cases which received serum treatment only 22 died, or but 26 per cent. It is unfortunate that in this series there were not as many control cases without serum as there were cases treated with serum. A mortality of 34 per cent is unusually low for plague, and possibly, if a comparison had been made with an equal number of controls, more of the additional cases would have developed septicemia and succumbed.

In the study of their tables a perhaps still more striking feature is developed. Of 8 cases treated with the Yersin serum on the first day of the disease before septicemia had developed all recovered. These were the only cases of this nature which were treated with Yersin serum. In India, as the statistics show, the majority of the patients are not brought to the hospital before the second day of the disease, and, as we have already emphasized, but little benefit can be expected from the serum treatment of plague unless the serum is employed before this time. Of the 24 cases which they treated with Yersin serum on the second day of the disease before septicemia had developed 17 recovered and 7 died, a mortality of 29 per cent, while of 24 control cases not given serum who entered the hospital on the second day of the disease and before septicemia had developed 10 died, a mortality of 41.6 per cent.

The results, therefore, seem to show, as the others related have, that if the serum can be given early enough in the disease, and if the infection is not too severe, a beneficial effect may be often obtained. The result of serum treatment in plague, however, is frequently uncertain, and it must be borne in mind that it is only within a narrow limit of time that its use in man as in animals is efficacious.

The more recent reports in the literature upon serum treatment of plague do not concern large series of cases. Armstrong in the plague epidemic in Australia treated 11 cases with serum; 10 of these recovered and 1 died; 5 other cases that did not receive serum also died of the infection.

De Faria, who used the serum both from the Pasteur Institute in Paris and from the laboratories at Berne, during an outbreak of 64 cases in Lisbon in 1920, states that the results were disappointing.

Allain in the recent epidemic of plague in northern Africa draws attention to the satisfactory results which followed large injections of plague serum, but does not give statistics.

Johns says that the early diagnosis and administration of serum in sufficient quantity has in late epidemics lowered the mortality to about 25 per cent, and that the percentage of recovery where treatment is established during the first twenty-four hours after onset of symptoms is in every way comparable to the results obtained by the use of antidiphtheritic sera. This statement seems to the writer too optimistic and would seem to apply particularly to the outbreaks of plague that have occurred in the United States and in South America, which have been of a much milder character than the epidemics frequently observed, for example, in the Far East.

Seeman in the treatment of 18 cases with serum in the New Orleans outbreak had only 3 deaths. From 120 to 200 c.c. of serum was injected and the doses were sometimes repeated.

Treatment in Pneumonic Plague.—In the treatment of pneumonic plague, however, serum treatment has given no favorable results, and it can only be stated that the serum in some instances has appeared to have prolonged somewhat the life of the patient.

In the early stages of the disease the serum appears to cause a fall in temperature and a temporary improvement in the general condition of the patient. During the recent Manchurian epidemic the fall in temperature usually occurred during the first three hours after the injection, and lasted for from six to twelve hours. Sometimes the temperature fell from 0.5 to 2.5° C. after the injection. After the fall, the temperature usually again suddenly rose. Sometimes following the injection the pulse became stronger. The injection of serum did not prevent the development or extension of the pneumonia to other lobes of the lungs unaffected at the time of the injection, nor did it prevent the development of septicemia. After septicemia had developed the serum seemed to exert no favorable effect whatever upon the patient. Only when given in a very early stage of the disease did it appear to prolong the illness.

Of 42 human cases of pneumonic plague treated with antiplague serum during the recent Manchurian epidemic, 33 received the first injection of serum within six hours after the first symptoms of the illness had appeared. The remaining 9 received injections of serum on the second day of the disease. All of them died of pneumonic plague. The injections were given both intravenously and subcutaneously. No difference in the course of the disease was observed with either of these methods. The quantities of serum injected varied from 100 to 1,700 c.c. All of the cases which were treated with serum during the epidemic died so far as is known, with the exception of 3 cases reported from Dalny, but in these 3 cases the International Plague Conference considered that the bacteriological diagnosis of the disease was not sufficiently definite. The general experience throughout the epidemic, therefore, was that no method of treatment was of any value in saving life, and that the serum treatment seemed only in a few instances to have prolonged the duration of the illness.

Selection of Serum.—In employing serum in the treatment of plague the physician should be sure that the preparation is a reliable one. Plague immune sera have sometimes been offered for sale in which the immunizing power is so small as to render them practically of no value in the treatment of the human disease. The preparation of a satisfactory plague immune serum is tedious, difficult, and expensive, since it requires a long period of time to immunize successfully the horse from which the serum is obtained, and the animal not infrequently dies during the course of such immunization.

Method of Testing the Immunizing Value of Serum.—Before using a serum in an epidemic of human plague it is well to have its immunizing power tested upon rats in the following manner: The doses of the diluted serum should be injected intraperitoneally, a blunt syringe needle being employed for the injections, and immediately after the rat should be inoculated with a 5 c.c. syringe needle dipped in a suspension of plague bacilli in bouillon (one 48-hour agar culture of a virulent organism to 5 c.c. of bouillon), the needle being thrust under the skin for its full length near the root of the tail and then withdrawn. The serum should, of course, be inoculated in various amounts, and the experiment should always be performed in duplicate or triplicate, two or three animals being employed for each dose of serum, and an equal number of controls. A good plague immune serum should save from fatal infection at least 50 per cent of the inoculated rats.

Varieties of Sera.—The variety of plague immune serum which is generally used is prepared from the horse by first the inoculation of killed cultures of the plague organism, and later by the inoculation of increasing amounts of living virulent organisms, and usually by filtrates of old bouillon cultures. A serum prepared in this manner is often spoken of as Yersin serum. Sera obtained in this way are at the present time generally acknowledged to possess the highest immunizing value. The method of preparation may be shortened by beginning with living virulent cultures in place of killed ones. Another plague immune serum has been prepared after the method of Lustig and Galeotti in which the nucleoprotein of the plague bacillus is inoculated subcutaneously and intravenously into the horse furnishing the serum. Terni described a method of preparing an antiplague serum which he believed was especially active against the plague toxin. The animal furnishing the serum was inoculated with peritoneal exudates from guinea pigs dead of plague and with the serum from plague buboes. Terni believed that these exudates contained aggressin. However, the writer has shown that the immunity obtained by the injection of natural plague aggressin is not of a different nature (so far as it concerns specific immunization) from that secured by the inoculation of living plague cultures, and hence the serum prepared in this manner has no advantage over one prepared by the inoculation of living organisms, as the results in man have shown. Of 111 cases treated with Terni's serum the mortality was 81.08 per cent, while of 112 parallel cases receiving no serum the mortality was 81.25 per cent.

Antitoxic Sera.—The plague toxin is an endotoxin. It differs somewhat from the toxin of the cholera or typhoid organism in that it becomes more easily set free from the bodies of the bacteria, but so far it has not been possible to prepare a satisfactory antitoxic plague serum for treatment.

Markl, Dean, Rowland and MacConkey have experimented with the idea of obtaining antitoxic plague sera either by using for the inoculation of the animal filtrates from old bouillon cultures, or by extracting toxins from the plague bacillus. So far these sera have not shown any advantage over those prepared by the usual method already described.

Rowland has prepared a serum in horses by inoculation of a nucleoprotein which he has obtained from the plague bacillus by a method which he characterizes as a sulphating process, dilute sodium sulphate or salt solution being used for its extraction. This serum was employed in India in 1913 for the treatment of human cases, but also showed no superiority over the Yersin plague serum.

Multivalent Serum.—Hetsch and Rimpau have performed experiments in preparing a multivalent plague immune serum, using nineteen different strains of the organism for the purpose. The value of such a serum was afterward tested upon rats. It was shown, however, that such a polyvalent serum possessed no advantages over a univalent one. The plague immune serum produced with one satisfactory plague strain will exert its anti-infectious action against all strains of the plague bacillus, no matter what their source, hence a plague polyvalent serum is not more or less effective in its action against any one of these different strains than is a univalent one.

Symptomatic Treatment

The patient should be kept in bed, given good nursing, and fresh air. An initial purgative is generally advisable. The fever should be treated by sponging every hour or two with warm or cold water. Antipyretic drugs, such as the coal-tar products, should in general not be employed, as the heart is frequently affected early in the disease. Stimulation is frequently necessary, and for this purpose digitalis, strophanthus and strychnin may be employed and seem in this disease more advantageous than alcohol. Thoulon has recently found digitalis of great value in treating myocarditis due to plague. In violent or very restless cases hyoscin is frequently of service. For the headache an ice-cap is preferable to drugs. Ice-bags or cold applications should be applied to the buboes. The general result of experience is that energetic treatment by caustics, mercurial inunctions, or early surgical interference is painful and produces no favorable change. In Hongkong the injection into the glands of a solution of perchlorid of mercury and carbolic acid was recommended as giving only temporary benefit. When softening or suppuration occurs surgical treatment by incision and drainage is called for, but nothing is gained by too early incision. Excision of buboes is of doubtful service and has often been followed by serious results, as a rapidly fatal septicemia. Stitt has recently emphasized this danger. All skin lesions and carbuncles should receive antiseptic treatment. Opium or hyoscin is sometimes necessary in the maniacal cases. The patient should be urged to drink plenty of water in order to secure abundant elimination through the kidneys. The urine should be frequently examined and any symptoms of aneuresis or acidosis treated by alkalis administered either rectally or intravenously as described in the Treatment of Cholera on page 727. For the vomiting, cold applications to the epigastrium may be used and relief is sometimes obtained by the administration of a saline cathartic. In severe hemorrhagic cases calcium chlorid may be employed. It is important to keep the patient prone in bed until the temperature has been normal for at least three or four days, otherwise death by syncope may result. The heart's action may remain weak for a long time after convalescence, and tonics and stimulants are frequently indicated. The diet should consist of broths and milks. Thompson believed that the internal administration of carbolic acid frequently produced beneficial results. In a series of 143 cases the mortality of the cases treated by him in this manner was 30 per cent. The drug was given in capsules, 12 gr. every two hours or 144 gr. daily. Carboluria rarely occurred if the drug was pure, and it is stated that this symptom was easily controlled by omitting several doses. Tincture of iodin, 5 drops every three hours by mouth, or the application of iodin locally to the buboes, or 7 minims of the tincture given in saline solution intravenously once in twenty-four hours, has been used extensively in the Maratha plague hospital in India, and its employment sometimes seemed beneficial.

THE SPECIFIC PROPHYLAXIS OF PLAGUE

A number of different methods of protective inoculation against plague have been described. Haffkine first recommended killed bouillon cultures. Killed agar cultures, killed sensitized agar cultures (with serum), extracts of the plague bacillus, and living, thoroughly avirulent cultures (true plague vaccines) have also been employed. There is no doubt that a higher immunity against plague infection may be obtained from the use of the living, avirulent cultures than from the killed organisms, and, in fact, while it is possible to immunize a high percentage of guinea pigs with living avirulent cultures, guinea pigs cannot be immunized against virulent plague infection with killed cultures. However, in practice, while this method may be the best for some groups of individuals where the preparation of the vaccine can be carefully controlled, it is not a method that can be generally recommended for large numbers of people during a widespread epidemic. When the prophylactic has to be prepared in exceedingly large amounts in the laboratory, only a method of employment in which the vaccine is fully sterilized is advisable, and the use of the killed bouillon or agar cultures of the plague bacillus, unsensitized, on account of ease in preparation, is to-day generally employed for prophylactic inoculation against plague. In India, Haffkine's method of inoculation is employed. Broth cultures are grown for six weeks at room temperature and heated for one-half hour at 65° C., and 0.5 per cent phenol is then added. When used within three months of the date of manufacture, a dose of 3 c.c. is recommended by the Bombay Bacteriological Laboratory. A vaccine made from 24-hour-old agar cultures, suspended in saline solution, and heated for one hour at 65° C., has also been employed for human immunization during epidemics. Leger and Baury, in order to do away with the local reaction following the subcutaneous injection of the plague vaccine, have suggested that it be administered orally after the administration of ox bile. Their experiments, however, are not sufficiently extensive to demonstrate that immunity may be acquired in this manner.

Numerous statistics which have been published in different parts of the world would appear to have demonstrated the value of protective inoculation in bubonic plague, and the opinion is rather generally accepted to-day that an active immunity produced by inoculation has a distinct influence of practical importance in the prevention of the disease. Haffkine's statistics, published in 1908, with reference to a very large number of antiplague inoculations performed in India, showed that inoculation reduced the liability to attack to less than one-third of what it was in the uninoculated, and that the recovery rate in the inoculated was at least double that in the uninoculated. The report of the Commission appointed by the Government of India to investigate the efficacy of protective inoculation against plague concluded that the evidence pointed decidedly to the value of vaccination, and that inoculation sensibly diminished the incidence of plague in the inoculated population, although the protection afforded was not absolute, and also that inoculation diminished the death-rate among the inoculated population.

Recently, Cadet and Gaide have reported upon the results of vaccination with Haffkine's prophylactic; 140,000 injections were made. The first dose of 1 c.c. was followed by a second of 2 c.c. twelve days later. The only definite conclusion arrived at was with respect to a series of cases of Phanri. Of 22 fully vaccinated cases, 12 died of plague, giving a mortality of 57 per cent, while of 27 non-vaccinated controls, 26 died of plague, giving a mortality of 96 per cent.

Mazzone reports that antiplague vaccination on a large scale arrested an epidemic among Arabs after it had caused 108 deaths in 173 patients among 2,350 Arabs not vaccinated, and 27 deaths in 93 cases among 11,836 Arabs that had been vaccinated. There were 12 cases of plague with 1 death among 7,110 Europeans inoculated with the vaccine; 850 individuals who had not been protected by vaccine also escaped infection.

Recent reports from the Bombay Bacteriological Laboratory, issued by Major Glen Liston since 1910, also give much evidence regarding the value of the inoculations. The following table compiled by Teague from the Indian records also speaks decidedly in favor of the value of protective inoculation.

COMPARATIVE MORBIDITY AND MORTALITY FROM PLAGUE AMONG INOCULATED AND UNINOCULATED

Inoculated					Not Inoculated				
Population	Attacks	Deaths	Incidence per 1,000	Case Mortality, Per Cent	Population	Attacks	Deaths	Incidence per 1,000	Case Mortality, Per Cent
118,148	941	371	7.96	39.5	321,621	11,041	8,695	34.4	78.6

Kiamil reported, in 1922, that the clinical signs in the course of a plague epidemic were very different among the vaccinated cases and unvaccinated ones, being much milder in the former. Among the vaccinated, numbering 8, no deaths occurred, but of 103 unvaccinated, 51 died. Baker, during the plague epidemic in 1920 in Uganda, where nearly 14,000 inoculations with Haffkine's antiplague vaccine were made, observed 53 deaths among those who had received the vaccine. These statistics demonstrate what numerous other statistics do that the protection afforded by inoculation is often inefficient.

McCoy has pointed out that there is no important evidence indicating that vaccination alone has ever controlled a severe outbreak of plague. Teague has also called attention to the fact that, while prophylactic inoculation diminishes the incidence of plague in human beings, and lowers the percentage of mortality in those that contract plague, it does not serve as a factor in eradicating plague permanently from a district or country, since the plague in rodents is not affected thereby.

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CHAPTER XXIV

TULAREMIA

George Blumer

In 1910 Pearse of Brigham City, Utah, described a local outbreak of a disease characterized by a painful bubo in the region of an infected insect bite, usually on the face or other exposed part of the body. The affected glands usually suppurated and the process was accompanied by fever of a septic type lasting from three to six weeks, associated with great prostration, and followed by slow convalescence. Subsequent investigations by Francis, Wherry and others have shown that the disease is due to an organism, Bacillus tularense, closely allied to the bacillus of bubonic plague. The parasite is transmitted by insect vectors; and the jack rabbit, the ground squirrel and other small animals serve as hosts. The disease is usually transmitted by flies, the common stable fly or the Chrysops discalis in Utah, but bedbugs and possibly other insects can convey it.

Treatment.—There is no specific treatment and the disease must be handled like typhoid fever. The buboes require incision and surgical care if they suppurate. Previous to this hot applications and anodynes may be required to relieve the pain. The patient should be kept in bed on a soft, easily digestible diet supplying 2,000 to 2,500 calories daily. The fever may be high and the disease often lasts for weeks, so that the patient must be protected against serious loss of weight. Free consumption of fluids is to be encouraged. If the fever goes above 103.5° F., tepid sponges should be used to reduce it. The bowels should be moved daily by enema or occasional purgation. Stimulants may be needed in the more prolonged cases.

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CHAPTER XXV

TREATMENT OF TUBERCULOSIS

HERBERT MAXON KING AND LOUIS HAMMAN

REVISED BY LOUIS HAMMAN

WITH SECTION ON HELIOTHERAPY BY JOHN H. PRYOR

GENERAL CONSIDERATIONS

The treatment of tuberculosis is in principle so simple that every intelligent layman can glibly recite the formula—rest, fresh air and food. Centuries ago a shrewd practitioner advised a young man with phthisis to get himself a cow and go up into the mountains. Physicians are fond of quoting this advice with an air implying that this preternaturally sage physician had thus summed up all the wisdom of the modern tuberculosis therapist. Some present-day practitioners in imitation of this admired example restrict their therapeutic efforts to similar laconic advice, telling the tuberculous patient to go to the country, take things quietly and eat lots of milk and eggs. The whole matter is apparently so simple as that. However, in this instance, as in many others, appearances are deceptive. I know of no other department of practice so generally mismanaged as the treatment of tuberculosis. The very simplicity of the principles beguiles the inexperienced and unwary into an attitude of assurance and security and yet the successful application of these simple principles demands more knowledge, more experience, more wisdom than to master the most intricate therapeutic technical procedure. To treat tuberculosis well a physician must know many other things in addition to medicine; he must, for instance, know human nature and how to mold it. He must study the personality of his patient as well as his disease and strive to strengthen character where it is weak, to protect it from insidious and undermining influences both physical and spiritual, to direct and guard the play of the emotions and to call forth an optimistic and confident cooperation. The fullest demands are made upon the best qualities of heart and mind.

The tuberculous need rest and fresh air and nourishment, but how are we best to bring, at this time, under these peculiar circumstances, to this particular patient, rest and air and food? You may have an excellent plan to follow, but the circumstances surrounding each patient offer an insuperable barrier to the application of any routine. Readjustment and compromise are constantly demanded and the working out of these adjustments and compromises is the test of the physician's skill.

I think it needs no detailed demonstration to convince physicians that the treatment of tuberculosis as now carried out by experienced and skillful practitioners is, at least in a measure, successful treatment. Even a casual comparison of results obtained to-day with the gloomy acquiescence to inevitable disaster aroused by a diagnosis of tuberculosis forty years ago shows that much. And it must be remembered that this changed attitude toward the prospects of recovery from tuberculosis depends entirely upon the application of the simple principles, rest, fresh air and food. We are as far to-day as we were forty years ago from a specific cure for the disease. Everything that has been accomplished rests primarily upon the hygienic-dietetic treatment of the disease. From time to time emphasis has been shifted from one to other details in applying the principles. Even now there is no general agreement about the details, but the principles remain fast.

When we speak of the treatment of tuberculosis we are accustomed to have in mind pulmonary tuberculosis, because this is the commonest form of the disease and because particular and widespread interest has centered about the treatment of this form. It has not been sufficiently understood, at least I judge so from what I see of practice, that the treatment which has proved itself so beneficial in pulmonary tuberculosis is equally beneficial, indeed perhaps more so, in other forms of tuberculous disease. I say more so because these other forms are more likely to heal under any treatment than is pulmonary tuberculosis and since the prospect of recovery is good they should be sought out and treated with especial care. I refer particularly to what are called surgical forms of tuberculosis. If a tuberculous lesion is localized and most of the tuberculous area can be removed, a large handicap is lifted from the body which is thus put in a more favorable position to cope with the remaining infection. This advantage is well shown in a comparison of the results of treatment in tuberculous peritonitis in males with the results of treatment in that form of tuberculous peritonitis associated with large pelvic tuberculous masses in females. When these large pelvic masses are removed, recovery almost always takes place. However, in surgical forms of tuberculosis, physicians too often stop their therapeutic endeavors with the operative procedure. This is obviously a false emphasis. Operation should not be looked upon as the last step of treatment but as the first, as an attempt to put the patient in the best possible condition to profit by hygienic dietetic care.

In the whole field of tuberculosis therapeusis, there is no question that arises more persistently nor any that deserves more thoughtful consideration than the question—What persons should receive tuberculosis treatment? Convincing statistics teach us that nine-tenths of the human race is infected with tuberculosis. This infection for the most part runs its course without giving signs of its presence. It may be detected by the searching aid of tuberculin, but happily most of those infected remain in good health and suffer no apparent ill effects. The difficult point in practice is that we possess no means to distinguish among the infected those who will remain well from those who will subsequently develop tuberculous disease. Further, there is no clear mark where tuberculous infection passes into tuberculous disease. The manifestations of tuberculous infection that our clinical methods detect are mostly the symptoms of gross disease. We are eager to discover ways to see more acutely into the progress of tuberculous infection so that we may detect when innocent infection threatens to erupt into active disease. This desire is as yet entirely unfulfilled and from what we know of the problem we can entertain no ardent hope of fulfillment in the near future. The shortcomings of our diagnostic insight should stimulate us to employ the methods we have to the limit of their applicability. If we do so we shall not go entirely unrewarded, for there are clinical manifestations of tuberculous infection that may be appreciated only by the vigilant and the wary. Commonly enough these slight symptoms are signals that warn of oncoming disaster and there is good reason to believe that heeding the signals may ward off the disaster.

The situation may be roughly illustrated by drawing two parallel lines and assuming the space below the lines to represent the uninfected, the space between the lines to represent the infected without symptoms of disease, the space above the lines to represent the infected with manifestations of disease which can be appreciated clinically. What happens between the lines is carried on in obscurity. We can sound this depth only with the aid of tuberculin, which tells us whether or not infection exists. But what interesting graphic charts our fancy can construct from the facts we observe when the infection projects into the clinical field! As I have said, in most of us the play of infection progresses beyond our view, but often circumstances carry it almost but not quite into vision. In some a favoring concurrence of events thrusts it boldly and prominently above the line of clinical demarcation to remain there or to sink again into slumbering obscurity. In others it comes into view gradually and hesitatingly, hovering, as it were, about the threshold, to disappear again or to advance slowly or swiftly but with fatal progress. In still others it appears and disappears at intervals, finally receding, to appear no more, or coming again more boldly and permanently into the light. As our knowledge increases we shall be able to look a little deeper into the darkness and interpret with confidence what now we can only surmise.

I may be pardoned for having stepped aside into the field of tuberculosis diagnosis when it is realized how intimately diagnosis and treatment are linked together. One of the most important demonstrations of the treatment of tuberculosis is that treatment is successful in proportion to the stage of the disease at which treatment is begun. The more limited the disease the better the outlook for recovery. This statement is so self-evident that it would seem unnecessary even to mention it. Yet, odd though it may appear, its obvious implications are often disregarded in practice. There are many reasons for this disregard. Prominent among others are a lack of diagnostic skill, a negligent optimism which refuses to see danger until confronted by a serious accident, failure to push investigation diligently when suspicion has been aroused and, very prominent, I should say, a lack of proper appreciation of the spirit of tuberculosis treatment and ignorance of the methods used in carrying it out. Many physicians labor under the misapprehension that sanatorium treatment and tuberculosis treatment are synonymous. It is only natural that the sanatorium should have come to occupy an imposing position in the mind of the physician who casually turns his thoughts to the treatment of tuberculosis. Its work has entitled it to this prominence, but he often seems to forget that the sanatorium is one way of carrying out tuberculosis treatment, perhaps the best way, but by no means the only way. A physician who has detected the early manifestations of tuberculous disease should not think of treatment in terms of sanatorium treatment or no treatment, but, having convinced himself of the accuracy of the diagnosis which implies the necessity for treatment, he must then decide how this treatment can best be carried out. The sanatorium should be considered as one important way of carrying it out, but if under the circumstances the sanatorium is inadvisable or unavailable then other methods must be devised. It is the judgment and skill the physician displays in making these decisions and in devising these other methods that mark the successful therapist.

After clinical tuberculosis has become well established, recovery is purchased at the expense of long and exacting treatment. I have already pointed out the importance of beginning treatment at the earliest manifestation of disease, but it might be suggested that we go even further than this and begin the treatment of infected persons before evidence of disease is established. The suggestion is pertinent and such a plan would no doubt be highly successful, indeed I may say that it has already proved its remarkable efficacy. Of course the infected cannot be treated in the radical way that those with tuberculous disease must be treated. Infection is far too prevalent for that. But any improvement in general living conditions which raises the health of a community to a higher level decreases the incidence of tuberculous disease. There has been a conspicuous fall in the death-rate from tuberculosis during the past sixty years. The curve of decline has fallen with extraordinary rapidity during the past twenty years. There is no general agreement among students of the disease about the relative influence of the various factors concerned in bringing about this decline. The problem is unusually involved, indeed it cannot be solved, so closely interwoven are the various factors. I need only point out that while better living conditions improve the health of a community they at the same time decrease the opportunity for infection. However, all students who have studied the situation are agreed that the remarkable improvement in living conditions that has come during the past half decade has been an important factor and many believe the most important factor in the decline of tuberculosis mortality. This improvement in living conditions is truly a hygienic-dietetic readjustment of the community. The remarkable efficacy of this readjustment has been demonstrated, but it has not yet accomplished all that is desired because tuberculosis is still a prevalent disease. If we could only find a way to distinguish among the infected those threatened by tuberculous disease! No sure way is as yet discovered but we are groping towards a path with some promise of success. We have come at last to that much abused and much misused conception, the pretuberculous. There is no precise scientific way to identify this threatening state of insecurity but we define it in the clumsy terms of empiricism. The chief practical result of this conception has been to establish camps, open-air schools, and colonies for delicate children, particularly for delicate children who have been exposed to infection. We cannot measure accurately the direct benefits of such treatment, but there is sufficient evidence to encourage us to believe that this is a fundamentally sound adventure and one that will prove highly profitable.

Before beginning a consideration of the principles of tuberculosis treatment I cannot pass by unnoticed an important though commonplace detail. I have tried to emphasize, and I hope successfully, that while the principles of tuberculosis treatment are simplicity itself yet their application is most intricate and difficult. I hope I have driven this point home because the whole difference between success and failure in the treatment of tuberculosis depends upon attention to trivial details. The patient must never be allowed to exercise the slightest choice in carrying out the physician's orders. Every order must be so clear and so specific that there is no latitude for personal interpretation. No heterodoxy can be tolerated; it must be absolute, blind allegiance or excommunication. It seems a bit absurd to make such a dogmatic statement when every exponent of tuberculosis therapy manages details in a different way. Still, while many roads lead to Rome, if you wish finally and safely to get there, you must implicitly follow the guide you have chosen. You would be little advanced towards the desired goal if your chosen guide discussed with you the relative merits of all the roads and contrasted their various lengths and the difficulties to be encountered upon each and then sent you forth into an inextricable maze with a genial and encouraging Godspeed. When a patient chooses a physician he implies confidence in him as a guide. The physician must not betray this confidence. He must take him along the road that he has followed with a thousand other patients and which he knows leads usually to a happy termination. As his experience grows he will ever seek to get around difficulties by a more pleasant path, but he will never send off his charge to explore such routes at his own risk. This is not a fanciful matter, it is a matter of tremendous practical importance. I have seen the most learned physicians fail as guides to tuberculous patients on account of their indecision and the vagueness of their advice. Their deep insight into the nature of tuberculous infection and wide acquaintance with all the accumulated scientific data and opinions about the disease and the exercise of an incisive critical faculty seem to paralyze decision. When confronted with a concrete detail that must be decided they vacillate before the vast array of possible choices their erudition presents. They will discuss the point in a scholarly way, but the patient departs confused and undecided. On the other hand, I have seen physicians of indifferent learning but stolidly tenacious of the little they had learned make admirable guides to tuberculous patients. Confident of their own knowledge, unshaken in their belief that their way is the best way, they deliver their advice in a precise, dogmatic, sometimes oracular, manner. There is no danger that the patient will misunderstand the directions or go away feeling that to disregard them is a venial fault. Any infraction of the rules becomes a deliberate, willful, grievous sin. Such a physician's more astute confrères smile and poke a bit of fun at him, but his patients get well. It requires only a commonplace imagination to conjure up an illustrative example. Suppose you had tuberculosis and after a period of rest with satisfactory improvement you ask your physician—Has not the time arrived when I may take a little exercise? Suppose he answers—Yes, yes, I think you may do a little but take things quietly and don't overdo. However, suppose he should say—Yes, the time has come when you are to take exercise. Beginning to-morrow morning you are to walk slowly on the level from eleven to a quarter past eleven. When you return from the walk you are to go to your room and lie down quietly until twelve o'clock. Do this and no more each morning until I see you again a week from to-day. In essence the advice is the same, in substance they are far apart. Which advice would you prefer? What I am trying to do is to enforce upon the physician in every possible way the necessity of giving specific and definite advice. And now I hope the way is clear to insist upon the one and only sure way to give specific and definite advice, namely, the physician who has charge of a tuberculous patient should give his directions in *writing*. I cannot decide whether the happy practice of writing directions is a greater benefit to the physician or to the patient. I do know, however, that both are greatly benefited by the practice. It makes the physician think clearly and express himself accurately. He must commit himself absolutely to a specific and definite program. All vague directions such as "take a little exercise," "rest a lot and take plenty of food," "never get tired," "see that the bowels move daily," etc., disappear entirely from his vocabulary. And what a boon to the patient! It is really shocking to think how many tuberculous patients have been cheerfully sent to their graves by such well-meant generalities as "get yourself a place in the country," "you had better go to Colorado," "you must take things quietly now and rest a lot," "see that you get plenty of rest and take milk and eggs."

The directions written by the physician cannot be too detailed. Every hour of the day should be covered, specifying the time to retire, the time to arise, the hours to lie down, the hours to sit out of doors, the hours to exercise. The kind of exercise, the amount and character of food and the medicine to be taken should all be noted. As a final instruction the patient is warned not to modify the orders in any way nor to do anything not mentioned in the orders without consulting the physician. It happens only too often that a physician is surprised to find how grossly a patient has misinterpreted his instructions or how much laxative, cough mixture or other medicine he has been taking without his advice.

A number of experienced physicians follow the practice of having patients keep a medical diary in which they record in detail their symptoms and how they spend the day. At each visit these records are gone over with comments and form the basis for changes in the orders. If the plan is followed seriously it proves to be invaluable. I urge its use. When a patient is ill the record is kept by a nurse or an attendant. A constantly reiterated objection to the method is that it makes a patient introspective and neurotic by fixing the attention constantly upon his symptoms. I can only reply that I have not found this to be true and in the instances in which I have used the plan I have not had a single occasion to regret it.

FUNDAMENTAL PRINCIPLES OF HYGIENIC-DIETETIC TREATMENT

REST

Of the three fundamental principles of tuberculosis treatment rest stands out as preëminently the most important. It is the crux of the whole treatment and the outcome of treatment depends chiefly upon the skill and wisdom with which rest is managed. By rest I mean not only sitting out in a chair or lying in bed but a state of mind as well as a posture of body. A human being is a complex mechanism and to rest it is a complicated procedure. While the principle is simple the application is difficult. I have said this before and the vital importance of keeping it in mind must be my excuse for saying it again and again. I may even be pardoned for quoting the trite injunction—"Do not treat tuberculosis, treat the tuberculous patient." Were it not for the complex personality of the tuberculous patient, the question of rest would be settled out of hand and there could be no further dispute about it. If we could imagine all tuberculous patients translated to a state of euphoria in which their happiness and contentment would reside in the supine enjoyment of the play of the vegetative functions, treatment would be spontaneous and thorough. We should then see such results of treatment as we could never hope for in fact. I am convinced that the most thorough treatment for tuberculosis, could we disassociate tuberculosis from the tuberculous patient, would be rest, complete, continuous, unvarying rest. I should like to fix in the mind of the physician the conviction that such absolute rest is the ideal treatment for tuberculosis and any departure from absolute rest a compromise with the tuberculous patient. The most obvious and commonplace considerations show the necessity for constantly making this compromise. In the first place such absolute rest would be synonymous with annihilation, it would be a living death. Even though rest were not absolute but enforced within the limits of the possible, still it could not be long endured. Life at such a price would not be worth the purchase. The reward of treatment is the promise that sacrifice will within a reasonable time restore a measure of activity. Again, the criticism is frequently made that patients though cured of tuberculosis are transformed by the treatment from active contributing members of society into lazy, cowardly, useless appendages. It is unnecessary to point out that this criticism is not a stricture upon the efficacy of rest in the treatment of tuberculosis but upon the effects of treatment on the tuberculous individual. Such considerations simply emphasize again the complexity of tuberculosis treatment, for treatment though highly successful from one point of view may yet be a total failure from another.

My insistence upon rest as *the treatment* for tuberculosis is the result of my own experience in the treatment of tuberculosis and my observation of treatment as practiced by others. I can briefly summarize and emphasize this experience by saying that I have never seen a patient injured by rest, whereas I have seen many injured by exercise. The older I grow the more persistently I repeat to myself, to student and to patient that rest is *the treatment* for the disease and exercise a compromise to be allowed reluctantly and grudgingly. The way we carry out treatment will depend upon our general ideas about the principles of treatment and our conviction of their efficacy. Therefore I should like as the first step in a presentation of methods of treatment to have this point firmly fixed in the reader's mind. Exercise is not a treatment for tuberculosis, it is a compromise we must make to personal and social demands of irresistible importance. When exercise *is allowed* it must be ordered not as a part of treatment but as an inconvenient necessity. Looking from this standpoint, and I think it is the correct standpoint, the physician will proceed with necessary caution in prescribing exercise, whereas if he looks upon exercise, and especially upon so-called hardening methods, as an integral part of treatment he will prescribe exercise rashly and injudiciously.

The conviction of the supreme importance of rest flows from empirical observation. It is a conviction forced by the hard blows of practice. I doubt if one could reach it by way of an analysis of the scientific observations upon the physiology of exercise and rest. Such observations are as yet too limited. There is a strong popular tendency at the present time to put all the favorable emphasis upon exercise. This popular tendency is a strong current for the physician to oppose when he preaches rest. Patients insist that rest will weaken the body, destroy the appetite, upset the digestion, change courageous cheerfulness into crabbed depression—in a word, undermine all physical and moral well-being. They are abetted by friends and alas too often by physicians. The difficulty is that experiences from a state of health are supposed to be exactly reproduced in a state of disease. How false such a supposition! Every one has felt in health the physical and mental exhilaration of a brisk walk on a cool November day. Poets have sung these delights. But who has revealed the lassitude and fatigue so characteristic of tuberculous disease? It is often passed by unnoticed and at least but clumsily described in medical writings. Fatigued before exercise is begun, there is no invigorating reaction but instead further fatigue and depression. Many a tuberculous patient can reveal the story as he looks back upon his experience when the disease came on before he was aware it had caught him. Indeed this sensation of fatigue so characteristic of the intoxication of tuberculous disease is one of our chief aids in directing the amount of exercise a patient is to be allowed. The patient must be instructed to appreciate its significance and be guided by its warning. As a matter of fact, rest does to the tuberculous exactly the opposite of what is feared from it. The relief and comfort that rest brings is inconceivable to those who have not experienced it. And it brings this relief most strikingly to the worn, tired tuberculous patient still well enough to be about and struggling vainly to relieve his lassitude and fatigue by exercise, spurred on by the memory of its delightful stimulation in former years. A fortnight in bed will often allay his fever, improve the appetite and digestion, put vigor into his tired mind and body and altogether bring about such a delightful transformation in bodily comfort and mental ease as exercise can hardly parallel to the soundest body. Physicians know and many grateful patients know that just such experiences come with rest under a variety of circumstances even when tuberculosis is not present. Rest is the natural cure for all conditions of fatigue and I know many persons who for years sought in vain for relief from the worrying and fatiguing demands of their daily life by strenuous excursions into the open and now bless the advice that taught them to enjoy the pleasures of rest and profit by it.

In addition to rest of the body as a whole, it is equally important to insist upon rest of the affected tissues. Physicians have long observed the benefits of rest to inflamed tissues and nature usually enforces it. In tuberculosis of the bone and joints, success in treatment depends largely upon prolonged immobilization of the diseased parts. The fact that they can be immobilized greatly enhances the prospects of recovery. Unfortunately all tissues affected by tuberculosis cannot be rested in this complete way, but any harmless device that may even partially restrict their activity is a powerful aid to healing. A discussion of the devices that are used to procure this desired result for various tissues must be sought under appropriate regional headings.

The views I have expressed about the fundamental importance of rest are views that are generally but not universally held. Some experienced observers not only allow exercise as a compromise but actually prescribe it as an important part of treatment. Although I have myself no sympathy with the method, it is only fair that I should present the claims of those who advocate it. The most ardent exponent has been Paterson of England. In this country it was enthusiastically championed by such a careful observer as the late Dr. Herbert M. King.

THE THEORY OF AUTO-INOCULATION IN TUBERCULOSIS

Regarding tuberculosis as purely a bacterial infection, an invasion of the body by pathogenic organisms, and the elaboration in the tissues and fluids of the body of toxins as the result of their growth and multiplication, the theories of Sir Almroth Wright applied to bacterial infections explain the many and various manifestations of the disease as it is met with clinically. The basic principle of the work of Wright and his collaborators during the past decade is expressed in his own words as follows:

> "No one recovers from an acute or chronic bacterial disease unless it be by the production of protective substances in his organism. No one acquires protection against disease except, again, by the production of protective substances; and, finally, no one lives in the presence of infection and repels that infection except by the aid of the protective substances in his blood."

On this theory, if we regard tuberculosis as fundamentally a bacterial infection, it is obvious that prognosis depends upon the capacity of the organism to develop specific protective substances upon those subtle chemical changes in the fluids of the body, which result in the elaboration and circulation of unknown but specific antibodies and which are always the product of the peculiar reaction to the stimuli furnished by the infecting agent itself.

Thus the anatomical lesion as demonstrated by the ordinary methods of examination is altogether of secondary importance; for, while death may ensue from mechanical causes, as, for instance, from hemoptysis, suffocation, etc., just as in typhoid it may result from perforation of the intestinal wall, this is the exceptional cause, a fatal termination usually resulting from an overwhelming toxemia beyond the capacity of the protective mechanism of the organism to combat.

The acute or active stages of the disease may then be explained by entrance into the circulating blood of overdoses of toxins manufactured at the seat of the infection, before and until the protective mechanism of the body has developed sufficient antibodies to neutralize their effects; and subsequently in favorable cases the subsidence of acute manifestations and the return to an appearance of normal health are explained by the presence in the blood of sufficient neutralizing agents, as a result of the stimulating action of the toxins, to offset and "bind" the latter. And, finally, convalescence is established when the protective mechanism has elaborated sufficient antibodies to produce an immunity and destroy the infecting microbes, all this irrespective of the character, extent, or location of the anatomical lesion.

A lesion so small as to be undemonstrable by ordinary methods of examination may develop and throw into the circulating blood enough specific poison to produce all the symptoms of an acute progressive tuberculosis and prostrate the patient, while, again, an extensive lesion involving both lungs and with considerable cavitation is often associated with every outward appearance of health and a sense of robust well-being.

In the former case, according to Wright's theories, the patient is suffering from excessive inoculations derived from the seat of the infection, to which his organism is incapable of opposing sufficient antibodies —excessive auto-inoculation. In the latter case one of two conditions has arisen: either the response to the stimulation has resulted in the production of sufficient protective substances to neutralize the toxins, or the lesions have become so walled off by impervious connective tissue formation as to prevent auto-inoculation, that is, entrance of toxins into the general circulation in sufficient doses to do damage.

Control of Auto-inoculation.—It has been found by long experience that patients suffering from acute manifestations of tuberculosis are much improved and their symptoms brought under control, in many cases, by rest in bed, that, having attained a normal temperature and other evidences of betterment, they may, if prematurely allowed to get up and move about, quickly relapse with a return of the acute symptoms which characterized the former attack. Again, it has been found that patients evidently progressing favorably and without active symptoms on limited exercise may very readily develop "renewed activity" with acute symptoms, following a sudden considerable increase of exercise.

These phenomena are very instructive and have led to the recognition of the principle of "controlled auto-inoculation," that is, using the patient's own organism for the elaboration in the body of bacteriotrophic substances for the production of a specific immunity to the infection from which he is suffering.

It has been found that by a careful regulation of rest and exercise auto-inoculation in a large number of cases may be very accurately measured and controlled, and in the cases in which this is possible it may be employed to inestimable advantage in treatment. It has further been found that, when auto-inoculation cannot be controlled, a fatal termination is inevitable.

It has long been recognized and has formed the basis of modern treatment of tuberculosis that, during the active symptoms of the disease, the patient should be kept at rest. With the subsidence of fever and other manifestations of an active process, more or less exercise, according to circumstances, may be permitted, and in the practice of a few therapeutists possessing the courage of their convictions exercise has been gradually increased to a point representing a reasonably hard day's manual labor. Otto Walther at Nordrach, for instance, who utilized walking exercise almost exclusively, frequently brought his patients up to twenty or more miles a day, through a carefully graduated increase from day to day. He found that such patients as could reach the higher grades of exercise improved much more rapidly and permanently than those who remained at rest or on very limited exercise, and were much better prepared to return to a self-supporting occupation after discharge.

In many institutions, both in this country and abroad, and in some instances in private and dispensary practice, a similar plan was followed, with, of course, individual modifications of one kind and another. It was popularly understood as a "hardening process." It served to keep patients busy, to occupy their time and their mind, to keep them from laying on useless adipose tissue, and to stimulate their appetite.

In a few institutions exercise was diverted into forms of useful manual labor, possessing to some extent an economic value.

But a satisfactory scientific explanation of the real value of exercise was not offered until Marcus Paterson of Brompton Hospital Sanatorium at Frimley, England, applying Wright's principle of auto-inoculation, with the assistance of Dr. A. C. Inman, discovered that there was a definite relationship between auto-inoculation induced by exercise (manual labor) and the condition of the patient as shown by the opsonic index, body temperature, weight, and the character and amount of the sputa. Furthermore, that a reliable control of the auto-inoculation was possible therapeutically by a system of graduated exercise (labor). All of the advantages formerly recognized as the result of exercise in the treatment of tuberculosis could thus be explained on the theory of active immunization effected by the introduction into the circulation of slowly increasing doses of toxin derived from the focus of infection and elaborated in the patient's own body.

Acting upon this principle, Paterson has developed an admirable system of graduated labor at Frimley, from which he has attained excellent clinical results. Wherever it has been adopted in other institutions, it has met with success exactly according to the strict adherence to the principles upon which the whole scheme is based.

If exercise or labor be introduced into the treatment of tuberculosis merely as a *diversion* for the patient, as a "hardening process," as a means of stimulating the appetite or promoting a healthy state of mind and digestion, or, worse still, as an economic factor, without the vitally important comprehension of its dominant function, that is, the production of auto-inoculations of specific poisons, then the system is almost surely doomed to failure. But, when the fundamental principle of its action is kept conspicuously in view, its therapeutic value has been repeatedly demonstrated, and without doubt it forms one of the most potent factors in the therapeutics of tuberculosis.

If any plan of graduated exercise be adopted, and it is doubtful if any such plan can be carried out to best advantage outside a sanatorium, it is of the first importance to recognize promptly the symptoms of an "overdose," an excessive auto-inoculation. Paterson has shown that the effects of treatment may be very accurately gaged by its influence upon:

1. The temperature.
2. The sputum.
3. The patient's feelings.
4. The appetite.
5. The weight.

These are quite similar, in fact, to the guiding signals in tuberculin treatment. The opsonic index may also be employed, but, owing to the experience and the time required to make index determinations, it is not a practicable method for ordinary clinical use, and, as the other methods are sufficiently accurate and always immediately available, it is quite unnecessary.

A patient upon increasing exercise should be under *constant supervision,* and should be familiarized with the danger signals of an "overdose." A failing appetite, a sense of malaise, or loss of weight when the latter is not above normal are significant symptoms, frequently appearing before the temperature rise and increase of sputum. They are indications for a reduction in the amount of exercise, though not necessarily for a return to "absolute" rest. A rise of temperature which does not fall to normal with thirty minutes' rest and a marked increase of sputum, or a distinct change in its character toward purulency, with an increase of cough, are more imperative signals and indicate *rest,* more or less complete according to the degree of the symptoms.

Paterson considers a mouth temperature of 99° or more, if attended by headache or malaise, an indication for "absolute" rest.

(The effect of exercise upon temperature, with especial reference to the physiological rise during and immediately following muscular exercise, has been discussed in another section of this article.)

It is the experience, in this country at least, that headache and a sense of malaise may be entirely absent with a temperature which clearly calls for rest, so that a patient's subjective symptoms by themselves do not form a safe and sufficient guide to treatment. Temperature, therefore, should be very carefully watched during the periods of increase in the exercise. For the purpose of accurate supervision a daily chart should be kept in all cases until the patient has reached the maximum grade, such a record having reference particularly to the points mentioned.

Relation of Hemoptysis to Exercise.—This is a question which has been by no means settled. It is comparatively rare that hemorrhage occurs during or immediately following exercise; it usually makes its appearance in ambulant cases during the night or early morning while the patient is at rest, and when the blood-pressure, as read by the sphygmomanometer, is lowest. No wholly satisfactory explanation has been advanced for this fact, although the theory is plausible that during exercise the muscular blood supply is considerably increased, and, with the consequent rise in peripheral pressure, the strain is taken off the visceral vessels, while during sleep the opposite condition obtains, with a considerable increase of pressure in the vessels of the pulmonary circulation. Be this as it may, it has for long been the practice to place the patient on "absolute" rest in the presence of hemoptysis, and this is no doubt a wise procedure. However, experience teaches that in most cases blood-stained or slightly discolored sputum, in the absence of other symptoms, may be safely disregarded and need not of itself interrupt the course of treatment by induced auto-inoculation.

Whatever plan of exercise be adopted, whether walking, manual labor, or systematic gymnastics, it is very necessary that it should be carefully graduated. The Frimley scheme as worked out by Paterson is interesting for its completeness and attention to detail. It probably admits of a more accurate control of exercise than any other which has been devised, although, unfortunately, it is not practical of application to all classes.

As a matter of fact, such work as patients do while under treatment is of very doubtful economic value. It is not always an easy matter to devise suitable labor for patients, and the time and experience necessitated by the supervision, which is indispensable, usually offset any profit which might otherwise accrue to the institution in which such a plan of treatment is carried out.

But its therapeutic value is indisputable, and its psychological aspect is not to be despised. A patient of unusual intelligence and of a certain temperament may bring his walking exercise up to twenty miles a day or spend his allotted time in selected gymnastic exercise and be content to note the improvement in his physical condition as a reward for his labor; but the average person likes to have some *tangible* result from the expenditure of his energy. Even if it is nothing more than a hole in the ground or a pile of kindling wood, he will the more cheerfully go to work the next day and derive a sense of satisfaction in the growth of the woodpile or the widening of the excavation.

The results are extremely gratifying in both cases, although the plan as here described has a somewhat limited scope.

It will be seen that the theory of the method rests upon the immunological conceptions of Sir Almroth Wright. However fascinating these conceptions may be, they are not supported wholly by fact and indeed as far as they relate to tuberculous infection facts are overwhelmingly against them. There is no evidence of the real existence of such an interesting play of immunological forces as Wright describes. All experimental studies of tuberculous infection and of resistance to tuberculous infection have failed completely to establish an important rôle played by immune bodies in the blood. This has been sufficiently emphasized elsewhere and here is not the proper place to review the evidence. However, the value of the method as a treatment for tuberculosis must be judged by its actual results and need not fall with Wright's pleasant conjectures. I am willing to admit that exercise does in some instances produce beneficial results. These beneficial results I should explain upon a different conception from the one advanced by Wright. In sluggish inflammatory lesions, circulatory changes (hyperemia) about the lesion often promotes healing. When the lesions are external such circulatory changes are often induced with benefit by the use of mildly irritating, stimulating, applications. This method is a very dangerous one, however, when applied to internal lesions for we have no way to control the reaction. It may do good in some instances, but it will certainly do harm in many by breaking out of the bounds we had meant to fix. To my mind the danger is greater than the possible gain. The results of Paterson and of King prove that the danger may be largely removed when the method is used under the most accurate and painstaking control. Perhaps under the guidance of such men most patients may go unharmed and some may be improved, but I am convinced that the general practice of such a method would lead to disaster. I can recall many individual instances in which exercise prescribed as treatment has led to irreparable injury. Until it is proved that exercise as a treatment gives far better results than rest, it is foolhardy to choose the dangerous instead of the safe course. It is needless to say that such proof has not been brought. Leaving aside all question of risk I still believe the evidence is strongly in favor of the value of rest as opposed to exercise in the treatment of tuberculosis.

Food

Our notions about how to feed the tuberculous patient are rapidly undergoing a great change. I might more truly say they have already undergone a great change, but I speak of the transition as now going on because dietary notions that have survived from the period of suralimentation cling tenaciously to the minds of many physicians and almost without exception to the minds of the laity. Milk and eggs and the treatment of tuberculosis are ideas so intimately associated that it is difficult to wring them apart. Evoke the idea tuberculosis and immediately the idea milk and eggs rushes upon the mind to mingle with it. I have no quarrel with milk and eggs as useful articles of diet in feeding the tuberculous. I am debtor to them for such service that I shall ever hold them in grateful esteem. What I quarrel with is the gross misplacement of their service. Because under certain circumstances milk and eggs are invaluable in feeding tuberculous patients, the notion has become prevalent that every tuberculous patient should eat milk and eggs. From this notion has followed the further extravagant notion that milk and eggs have some peculiar virtue in the treatment of tuberculosis quite aside from their nutritive value. There is also a tendency to judge the favorable progress of a tuberculous patient in terms of pounds gained. Of course there is some justification for these prejudices else they would not be so firmly held, but they hardly deserve the preëminent importance often attached to them.

Loss of weight is one of the characteristic symptoms of tuberculosis, a return of appetite and gain in weight is one of the most obvious signs of returning health. This contrast no doubt led to the zealous efforts that have been made to force this encouraging symptom even though the patient's inclination rebelled. The reward of such zeal is often the striking appearance of improvement, encouraging to patient, physician and friends. A gain in weight that comes with subsidence of tuberculous disease is necessarily a mark of improvement, but that a forced gain of weight necessarily acts beneficially upon the tuberculous disease is far from proved. The state of nutrition of the patient is sometimes used synonymously with resistance to tuberculous disease. I have heard the matter put in words somewhat like these: a person gets run down, his resistance is lowered and the disease spreads; by resting and taking milk and eggs his resistance is raised and the disease is brought to a standstill. Such a naïve conception of the state of affairs is commonly held although there is no evidence to support it. It would be a great satisfaction indeed could so complicated a matter be justly compressed into such simple and convenient phrases. However, any one who has the slightest knowledge of the behavior of tuberculous infection in animals or indeed of the clinical course of tuberculosis in man is aware that resistance to infection or to the progress of established disease depends upon many factors, most of them not at all understood, and that even among the factors about which we know something the state of bodily nutrition does not rank very high. But it is not necessary to draw an argument from the speculative field of resistance to tuberculous infection or disease. An observant glance at ordinary daily experience will serve as well. Glance at the patients you know who have recovered from tuberculosis. Do the portly or even the robust predominate? I believe you must allow that they do not. Indeed in some communities particularly marked by the presence of a large number of tuberculosis recoveries it is noteworthy, and has often been commented upon, that the majority of the recoveries are spare men of delicate habit. One might with much show of right argue that a lean body is an asset in the fight against tuberculosis. It is certain that a fat body is a handicap. I remember reading years ago, but I cannot recall either the article or the author, some bitter yet facetious comments upon overfeeding in tuberculosis. The author deplored the unwarranted extravagance that was prevalent in building up tons of worthless fat at an enormous cost. I do not wish to have the appearance of rushing towards the opposite extreme and of advocating entire neglect of nutrition in tuberculosis. Feeding the tuberculous is a serious and an important problem, demanding careful consideration and much skill of the physician, but it is the same problem that is met in other infectious diseases. The problem is more pressing in tuberculosis simply because tuberculosis is longer drawn out than most other infections. In pneumonia, a disease of short duration in which the siege is quickly won or quickly lost, feeding is hardly a problem at all. It is an almost negligible feature of treatment. In typhoid fever, a longer and therefore a more emaciating disease, feeding at once becomes a matter of first importance. And in this respect the relation that typhoid fever bears to pneumonia is similar to the relation that tuberculosis bears to typhoid fever. It is interesting and instructive to compare the results of treating typhoid fever by modern methods with the results obtained under the older starvation plan in vogue twenty years ago. It is not uncommon at the present time to see patients pass through a sharp attack of fever of five weeks' duration with little or no loss of weight. What a contrast their convalescence is to the slow recovery of the pitifully emaciated and fever-eaten victims of former years. And yet I think it would be difficult to show in a conclusive way that the mortality of the disease or even the incidence of complications has been materially reduced.

What I wish to impress is that feeding in tuberculosis, although of the greatest importance, is still in principle very simple, really almost a matter of common sense. Food has no subtle nor specific effect upon the disease, but is of importance only in its relation to the well-being of the tuberculous patient, not in its relation to the tuberculous disease. Milk and eggs are expedients often desirable, sometimes indispensable, but they must not be confounded with remedies for the disease and looked upon as necessary parts of treatment.

I have already said that improvement in tuberculosis and gain in weight do not always go hand in hand. That they are usually associated depends upon the fact that gain in weight follows improvement and not that improvement follows gain in weight. However, even though gain in weight has no direct effect upon the course of the disease, still it often reacts favorably upon the tuberculous patient in quite another way. It is important not to slight nor belittle this effect. Since gain in weight is usually an early and often the earliest sign of improvement, it is a tangible source of encouragement to the patient, the physician and the friends. Estimate, if you dare, how far its influence may reach in this direction, particularly if the stage has been skillfully set for its appearance. We note this influence under all manner of circumstances, not alone in the presence of tuberculosis; and if you allow sufficient finesse in the execution, a highly successful and generally applicable plan of treatment could be practiced upon the simple principle to build up the undernourished and to pull down the overnourished. Perhaps an almost obvious warning is unnecessary. If gain in weight is too much insisted upon, discouragement may follow its failure to appear. A physician must therefore be guarded in the mark he sets for the patient's aim, but often the prospect of what may be gained makes it worth while to run some risk.

While the feeding of the individual well-to-do patient often taxes the ingenuity of the physician, it presents no problem in nutrition. The food they are offered supplies all the requirements of a satisfactory diet, if they will but eat it. The energy requirement, the nitrogen requirement and the salt and vitamin requirement are all met. In institutions where a large number of patients are fed and economy must be practiced, the problem of furnishing a suitable diet is quite different. Not only must the food be satisfactory from the standpoint of nutritive factors, but also it must be prepared and served in an acceptable way. The problem is particularly difficult in America, where not only individual tastes differ so widely, but where there are commonly brought together patients of various nationalities, each with his peculiar dietetic habits and prejudices, and, with hardly less marked differences, patients from the many widely separated sections of our own country. Add to this the undeniable fact that the act of preparing, cooking, and serving food is far from being highly developed in America, and the difficulties incident to feeding a more or less large group of invalids of this class over a protracted period of time become apparent.

During the more acute phases of the disease the patient, if left to his own initiative, will seldom overeat. Loss of appetite, anorexia, and gastric disturbance characterize active tuberculosis, and these symptoms, associated as they are with a general inhibition of nutrition, are frequently a stumbling block to dietetic treatment. Likewise, in slowly progressive, apyretic tuberculosis of long standing, the desire for food is so lacking that the efforts of the physician must be directed toward urging a sufficient amount rather than otherwise. It is at the beginning of convalescence, when there has become established a more or less well-marked immunity to the toxins of the disease, that the danger of overeating is a practical one. Frequently attention is first called to the matter by phenomenal weight gains, and even then there is a very natural disposition to look with satisfaction rather than suspicion on what should really be taken as a warning. Emaciation is a characteristic symptom of tuberculosis, to combat which every effort should be made to improve nutrition, and to introduce into the body a sufficient amount and a well-balanced ration; but it must be borne in mind that nourishment depends upon assimilation, and that so long as the disease is actively progressive the ingestion of even large quantities of food will fail to help matters to any appreciable extent, and if given to excess only impose an additional burden upon the organs of elimination already overtaxed. A small, well-proportioned diet adapted to the individual will at such times do more for the patient than can possibly be expected from a diet which is in excess of his enfeebled powers of assimilation.

A suitable diet for a patient without fever and progressing favorably does not differ materially from a suitable diet for the same person in health—with this exception, that in a tuberculous invalid much under weight a somewhat more generous ration is indicated than would be required for a healthy person taking a like amount of exercise. Increase in exercise both in health and in the presence of a tuberculous lesion demands a corresponding increase in food. Generally speaking, this demand is indicated by an increased appetite and a greater relish for the proteid elements of the diet, particularly for the proteids of animal origin.

The actual food requirements in any individual case can, with a little pains and experimentation, be worked out satisfactorily, but, as individuals differ in their food requirements within such wide limits, it is not practicable to apply any dietetic standard to an individual case without first determining the actual conditions which govern the particular case.

Observation over a considerable period of time and in a large number of cases shows that the *average* food requirements differ very little under like conditions. The same is true as to the diet constituency, although this differs somewhat in different countries owing to long-established national dietetic habits. For instance, in Germany, according to Voit, Rubner, and others, a considerably larger proportion of carbohydrates and a correspondingly smaller proportion of fats are consumed by the average person in health than is the case either in England or America. In the latter especially fats form a much larger part of the ration of the average person. There is less difference in the *average* protein constituency of the diet in different countries, although the source of the protein is more variable.

But, while *averages* are so similar, individuals present marked differences in their requirements, as has been said, and often without any apparent cause. It is a matter of common experience to see certain patients improve in all respects and regain or pass their normal weight upon a diet which will be quite inadequate to maintain weight and improvement in other patients, to all appearances of the same class and in the same condition. It is, therefore, quite out of the question to lay down rules which shall govern the amount of food or even its constituent proportions, and expect such rules to be generally applicable to individuals irrespectively. The problem must be worked out in each case and studied carefully in order to obtain the best results.

The following general rules have proved of value to the author in arranging dietaries for various classes of tuberculous invalids:

1. Men of the same respective age and weight seem to require a larger diet than do women.
2. All other conditions equal, a larger diet is apparently required by persons under thirty years of age than is the case after that period.
3. The laboring classes, that is, those who earn their living by muscular work, require more food than is the case with those living a more sedentary life, and in a certain measure the dietetic habits necessitated in the first place by occupation persist after occupation distinctions are removed.
4. The urban dweller consumes a larger relative amount of animal food and therefore derives a larger percentage of his energy from the protein constituent of his diet than is the case with the country dweller. This, of course, applies only to the higher orders of civilization.

With these points in view and bearing in mind the wide individual variations which occur in all classes, we may assume for present purposes the following standards, applicable to ambulant cases of comparatively quiescent tuberculosis under sanatorium treatment:

1. For the young adult men of the "working class" on very light exercise from 2,800 to 3,200 calories, of which from 110 gm. to 125 gm. shall be protein.
2. For the same class on five or six hours vigorous exercise (sawing or chopping wood, working with shovels, pickaxes, barrows, etc.), from 3,100 to 3,600 calories, of which 125 gm. to 140 gm. shall be protein.
3. For women of this class 200 calories and approximately 10 gm. protein may be deducted in each case.
4. For young adult men whose occupation has been more sedentary, for example, clerks, bookkeepers, tailors, students, etc., on moderate exercise (walking from one to three hours daily), 2,600 to 3,000 calories, of which not over 115 gm. need be protein.
5. For women of this class not to exceed 2,500 calories and 100 gm. protein.
6. For older patients a slight reduction in calorific value and a considerably lower protein constituent are desirable in each case.
7. For the country dweller a somewhat larger bulk, without increase in protein value, is usually desirable, all other conditions being similar, than is the case with the patient from the city.

As has been said, individual variations are marked. Occasionally patients have been known to do well and gain weight on a diet as low as 1,800 calories with only 80 or 90 gm. protein. More rarely others thrive, without digestive disturbance or other evidence of overeating, on a diet as high as 4,000 calories over a considerable period of time. In the latter case the increase is chiefly in fats and carbohydrates. Such a diet in any patient on restricted exercise, especially if there be a proportionate increase in proteids, is almost certain to work mischief eventually, and in the great majority of cases should be regarded as excessive. A patient who in normal life is accustomed to hard manual labor and a correspondingly large diet will, of course, more easily accommodate himself to such a diet (a return to his accustomed amount of food) as convalescence proceeds and his exercise is increased than is the case with patients whose former occupations have been more sedentary and whose diet has corresponded. In the former class nothing is to be feared from a ration which would almost certainly prove excessive in the latter, even while both are on the same allotment of exercise.

On the whole, however, the somewhat flexible standards given above are quite generally applicable and have proved safe as working bases over several years and with large groups of patients. They correspond closely with the standards worked out by Bardswell and Chapman in England, and do not differ materially from those which have been found satisfactory for healthy communities both in England and America.

They apply, of course, to that large class of tuberculous patients which is ambulant and free from serious complications, which in fact does not differ essentially, so far as diet is concerned, from the same group in health. The special dietetic requirements of the far-advanced, acute, and seriously complicated class of tuberculous invalids will be considered separately. Having determined, then, approximately the amount and chemical constituency of a suitable diet, it remains to so construct it that it shall satisfy the taste and not exceed the purse of the patient, and it is here that the ingenuity of the dietitian or the physician is brought to the test. It is one thing to prescribe a suitable diet in terms of proteids, fats, and carbohydrates, and quite another to construct such a diet in a manner to meet the individual requirements satisfactorily.

It is a commonly observed fact that among the poorer classes of wage earners there is a relatively extravagant table with a comparatively deficient nutritive value. This is due to a lack of judgment in the selection of material and skill in its preparation. The cheaper cuts of meat and all vegetables require skill, experience, and some talent in their preparation for the table, if their full nutritive value is to be secured, and if they are to be presented in a form most attractive to the palate. The more expensive cuts of meat require much less skill and time on the part of the cook. The housewife in the families of the poor, as a rule, lacks not only the necessary skill, but has too little time, aside from her other manifold and arduous duties, to make herself proficient in the culinary art. As a consequence she selects such foodstuffs as require the least time and skill in preparation, and in so doing increases the cost of the ration. Thus it comes about that, when tuberculosis develops among this class, the physician, conscious of the difficulties in the way of prescribing a mixed diet which shall meet the requirements, is almost forced to prescribe eggs and milk in quantities sufficient to make up the necessary calories. Undoubtedly a well-balanced mixed diet, properly prepared, would be much more efficient, and, with intelligent buying, much less expensive. It is true that milk possesses in itself all of the nutriment necessary to the support of life in man, and in infancy and early childhood is the ideal diet. Moreover, when reënforced by eggs, it constitutes a food which will suffice for the adult, but it is by no means a satisfactory ration for the adult even when so reënforced, and if persisted in it will work serious mischief with the functions of digestion, and make a return to a normal diet a difficult matter.

In the families of the poor, however, and among tuberculous invalids of all classes, in certain stages of the disease, milk or raw eggs or both constitute the most ready and effective means of reënforcing an otherwise deficient dietary. Used with judgment and discretion, and bearing in mind that a return to a normal mixed diet, as soon as it is possible to do so, is a most important desideratum, milk and eggs may properly be considered the chief auxiliaries to diet in tuberculosis.

Sources of Food Supply.—The protein in a normal mixed diet for a man on moderate exercise constitutes about one-sixth of his total food energy as estimated in calories—for example:

Protein	125 gm. =	500 calories
Fats	125 gm. =	1,125 calories
Carbohydrates	400 gm. =	1,600 calories
	Total,	3,225 calories

Analysis of a large number of individual diets approximating such relative proportions and total amount of food shows that on an average about 75 per cent of the protein is derived from animal sources and 25 per cent from vegetable sources. When starch digestion becomes impaired, as is frequently the case in tuberculosis during the stages when exercise is much restricted, there is usually a falling off in the amount of carbohydrates consumed out of proportion to the total lowering of the diet. In such cases a larger percentage of protein is derived from animal sources, while, of course, among many individuals habit and taste modify the relative proportions in both directions. But on the average the relation will be found to approximate 75 to 25 very consistently, in this country at least.

Butchers' meat furnishes about 20 to 25 per cent only of the total protein in an average mixed diet. Where milk and eggs are regularly taken with the meals, they supply the larger part of the remaining protein to be accounted for as derived from animal sources. In America, except in the coast fishing towns, sea food comprises an insignificant article of diet—a fact which is to be deplored, since, if it is properly prepared, fish is a most wholesome and inexpensive article of food.

Of the protein derived from vegetable sources in a mixed diet, such as that described, the great part is supplied in bread, cereals, and puddings. The fats of such a diet are derived chiefly from butter (or its equivalent), cream, meat fat, either in the meat as served or as used in the preparation of other foodstuffs, and eggs. "Drippings" and margarin as substitutes for butter have almost the same nutritive value as the latter, and in the construction of an inexpensive diet are employed in some sections of this country and somewhat more extensively in England.

The carbohydrate portion of the diet is, of course, derived almost entirely from vegetable sources, although when considerable quantities of milk are taken it furnishes an appreciable amount of this constituent. Cane sugar is almost a pure carbohydrate, and can be reckoned gram for gram. Bread, cereals, the legumes, and other vegetables constitute the great bulk of this important constituent of the diet.

More than one-half the total calories of a normal and well-balanced ration should be supplied in the carbohydrates. It is, therefore, important that vegetables, from which the greater part of this constituent of the diet is derived, should be selected with judgment and carefully prepared and cooked. It is quite as much an art to prepare vegetables properly for the table as it is in the case of meat and fish. As commonly served in hotels, boarding houses, institutions, and even in private families, they are usually unattractive to the taste and often indigestible, and for this reason the carbohydrate content of the diet is often found to fall below the standard of highest efficiency.

In many of the diet "cures," which have been so highly developed in Europe, particularly in Germany and Switzerland, the ingenious preparation of vegetables and the skillful combination of varieties make it possible to raise the amount of carbohydrates to constitute three-fourths or more of the total calories required, thus permitting a corresponding lowering of the proteins, and still to maintain a highly palatable and very efficient diet.

In the dietetic treatment of tuberculosis too little attention has been given to the value of carbohydrates, and too much stress laid upon the proteins and fats.

Preparation of Food.—The physician who essays to treat tuberculosis should not consider it beneath his dignity to acquire some knowledge (theoretical at least) of the culinary art. He will do well, in fact, to familiarize himself with the various cuts of meat, their relative cost and nutritive value, and to know how they should be prepared and cooked. No less should he be competent to supervise the cooking of vegetables.

The most choice and expensive cuts of meat may be rendered insipid to the taste and greatly reduced in nutritive value by ignorance or carelessness in cooking. The same is true of poultry.

Meat or poultry roasted at a moderate even temperature and not properly basted will come out of the oven dry, tough, and tasteless, with the result that it fails to appeal to the appetite, not to speak of the actual loss of substance which it suffers. To roast or boil meat or poultry properly it should be subjected first to a high degree of temperature—for example, 400° to 500° F. in the case of roasting, or to boiling water in the case of boiling—such a heat as will insure the quick formation of a "crust" on the surface, which prevents the juices from escaping and thus not only retains the flavor but the tenderness of the meat.

As soon as this is accomplished, which in fact requires but a few minutes, the temperature should be reduced to not above 190° F., where it should be maintained until the joint or the fowl, as the case may be, is thoroughly cooked. This requires from thirty-five to forty minutes per kilogram (seventeen to twenty minutes per pound) of the meat to be cooked. In the case of roasting it is best to use a skewer over a dripping pan, and it is very desirable to see that the joint or the fowl is frequently basted during the process. Skillful cooks accomplish this by fastening pieces of meat fat to the surfaces of the roast and turning the skewer several times during the cooking.

In broiling steaks and chops the same principle is to be observed—exposure to a hot fire until the surface is as it were sealed, and then to a lower temperature to allow of the proper cooking of the interior without burning the surface or permitting the juices to escape. The broiling or frying of poultry or fish requires somewhat less care and skill. There is a traditional prejudice against fried foods of all kinds, but particularly fried meats, which is very general. However, in the case of meats, if they are fried over a hot fire and as far as possible in their own fat, there is less objection to this method than is generally supposed, and often it appeals to the palate, especially as a grateful change from the routine methods. In the case of certain poultry and fish it is preferable to other methods and quite unobjectionable from the point of view of efficiency.

In cooking vegetables there is an infinite variety of attractive methods and combinations, which a skillful and intelligent cook will employ. The most common fault to be found with vegetables as they are served is that they are either underdone, and, therefore, indigestible, or allowed to remain so long in the oven, the pan, or the pot that they have lost all flavor and a good share of their substance.

The making of highly palatable and nutritious purées by various combinations of vegetables is a culmination of the culinary art to which few American cooks have attained; yet the recipes are simple and inexpensive, and their value as a feature of diet in disease is so great that they merit a more widespread popularity. A cook who understands their preparation will be able through their employment to keep up the carbohydrate factor of the dietary, as otherwise it is quite impossible to do.

Seasonal Changes in Dietary.—Theoretically there should be a lowering of the fats and, to a less extent, the proteins of the diet with a corresponding increase in the carbohydrates during the warmer months. As a matter of fact, there is less change in the relative constituency of the average diet than might be expected. The sources of the food supply change, of course, but it is found that there is no constant variation either in the total calories, the chemical constituency, or the relation of animal to vegetable protein. This fact is observed among groups of healthy individuals as well as among the tuberculous when left to their own initiative.

In the season when fresh vegetables and fruits are easily obtainable at small cost there is a tendency toward a higher carbohydrate content, but this is transitory, and the ordinary relation is quickly reëstablished in the absence of special effort to the contrary. There is, however, a natural diminution of butchers' meat in the rations of all classes during the very hot weather. This is recognized by patients and healthy persons alike, and should be heeded in constructing a summer diet for a tuberculous invalid. Fish is an especially appropriate substitute at such times, but great care must be exercised in purchasing and shipping fish in the warm weather, owing to its rapid deterioration—to avoid which it must be kept at a very low temperature to the moment of cooking, and even then it is unwise to ship it long distances in the hotter months.

Number and Arrangement of Meals.—In a large part of this country, especially in rural districts, and almost universally among the laboring class, it is customary to serve the heartiest meal in the middle of the day, and this is the practice, no doubt a wise one, in most sanatoriums for the treatment of tuberculosis. Patients should retire early, and to do so soon after a hearty meal is not conducive to rest or sleep.

In private practice, among those who are accustomed to dine in the evening, it is perhaps permissible to continue the arrangement of the meals to which they are accustomed; but even among this class, if it can be done without too great inconvenience and protest on the part of the patient, it is better to change the order and prescribe dinner at noon, and a lighter repast in the evening. "Afternoon tea," which in England is such a universal affair, is not very common in America. There can be no objection to it, however, provided it does not interfere with appetite for supper.

Ordinarily three meals a day suffice for all purposes. They should be punctually and regularly served, and the time given to each should be ample—thirty minutes each for breakfast and supper and forty minutes for dinner is none too much time to allow. Patients should be instructed to be deliberate and to masticate their food thoroughly in order to insure the greatest efficiency of the diet.

Variety.—In arranging a dietary for the tuberculous invalid it is of the first importance that sameness and monotony, both in the preparation of the food and in the material selected, should be avoided. A menu, however attractive in the first instance, which is repeated at regular and short intervals with persistent routine soon becomes tiresome and repugnant. Each meal should, as it were, come as a surprise to the patient—at least so far as the midday and evening meals are concerned. A patient with a very indifferent appetite is thus often tempted into taking, without coercion, a sufficiently substantial amount of food. Even a healthy individual, if he knows beforehand what each day of the week is going to bring him for dinner, is very apt to lose all zest for the meal before he sits down to the table.

It is a well-known principle, and one which Pavlow has demonstrated on dogs, that appetite and a relish for food enhance manifold the digestion and assimilation functions, and it is certainly not time wasted to spend thought upon any arrangement which is calculated to stimulate the desire for food.

As has been said, the construction of an efficient and at the same time an economic diet is a problem somewhat difficult to solve. It requires a careful inquiry into the relative food values and cost of the various articles on the market and some knowledge of the culinary art. It is a perplexing problem even in the home kitchen under the management of an intelligent housewife, but is much more difficult and complicated in institutional practice.

Bardswell, of the King Edward VII Sanatorium in England, has worked out a scheme which he has found to meet the conditions both as to efficiency and economy in a very satisfactory manner. He arranges a bill of fare for the month, with such articles of foodstuffs as the markets afford at the season, from which bill the daily menus are prepared. The average individual portion is indicated on this list, so that the cook may make sufficient allowance in the preparation of the meal with the minimum of waste. The following example is a copy of one of these monthly bills of fare actually employed (September, 1911). The portions indicate averages from which individuals vary in one direction or the other to some extent. It is a fairly generous diet, representing something over 3,000 calories. It will be noticed that a somewhat larger portion is allowed for men than for women:

Patients' Dietary—Bardswell

Diet "A"—Men			*Diet "B"—Women*		
Breakfast			Breakfast		
Porridge with Milk	2 oz.	= 56 gm.	Porridge with Milk	2 oz.	= 56 gm.
Bread	2 oz.	= 56 gm.	Bread	1½ oz.	= 42 gm.
Butter	½ oz.	= 14 gm.	Butter	½ oz.	= 14 gm.
Eggs	1	= 28 gm.	Eggs	1	= 28 gm.
Bacon	1 oz.	= 28 gm.	Bacon	1 oz.	= 28 gm.
Tongue, brawn, etc.	1 oz.	= 28 gm.	Tongue, brawn, etc.	1 oz.	= 28 gm.
Herrings	1	= 28 gm.	Herrings	1	= 28 gm.
Luncheon			Luncheon		
Milk	½ pt.	= 490 gm.	Milk	½ pt.	= 490 gm.
Bread	2 oz.	= 56 gm.	Bread	1½ oz.	= 42 gm.
Butter	½ oz.	= 14 gm.	Butter	½ oz.	= 14 gm.
Meat	3 oz.	= 84 gm.	Meat	2½ oz.	= 70 gm.
Pudding	5 oz.	= 140 gm.	Pudding	3 oz.	= 84 gm.
Dinner			Dinner		
Milk	½ pt.	= 490 gm.	Milk	½ pt.	= 490 gm.
Bread	2 oz.	= 56 gm.	Bread	1½ oz.	= 42 gm.
Butter	½ oz.	= 14 gm.	Butter	½ oz.	= 14 gm.
Meat	3 oz.	= 84 gm.	Meat	2½ oz.	= 70 gm.
Pudding	5 oz.	= 140 gm.	Pudding	3 oz.	= 84 gm.
Potatoes Greens Afternoon Tea	q. s.		Potatoes Greens Afternoon Tea	q. s.	

The cost of raw food material in this schema did not (in 1911) exceed 1/6 (36 cents) per person per diem.

In this country a very satisfactory diet for the ambulant, uncomplicated case may be supplied at not to exceed 30 cents per person per diem for raw food material, and in some sections of the country where moderate and low prices prevail the cost of the same diet may fall as low as 25 cents.

The following menus for several days are taken from records of one division of Loomis Sanatorium (Annex), where they were actually employed with satisfactory results from every point of view:

Annex Division Menus for One Week—Cost per Person per Diem, 30 Cents

	First Day	
Breakfast	Dinner	Supper
Oranges	Soup	Boston Beans
Shredded Wheat	Fricasseed Chicken	Catsup
Sausage	Tomatoes	Chocolate Cake
Corn Bread	Mashed Potato	Marmalade
Bread—Butter	Ice Cream	Bread—Butter
Coffee—Cocoa	Bread—Butter	Cocoa—Tea
Milk—Cream	Milk	Milk
	Second Day	
Bananas	Soup	Creamed Dried Beef
Oatmeal	Roast Beef	Baked Potato
French Toast	String Beans	Apple Sauce
Maple Syrup	Boiled Potato	Bread—Butter
Bread—Butter	Rice Pudding	Cocoa
Coffee—Cocoa	Bread—Butter	Milk
Milk—Cream	Milk	
	Third Day	
Stewed Pears	Soup	Corned Beef Hash
Cream of Wheat	Boiled Lamb	Peaches
Bacon	Rice	Spice Cake
Graham Muffins	Peas	Bread—Butter
Bread—Butter	Steamed Pudding	Cocoa
Coffee—Cocoa	Bread—Butter	Milk
Milk—Cream	Milk	
	Fourth Day	
Prunes	Soup	Cold Sliced Meat
Oatmeal	Roast Beef	Fried Potato
Griddle Cakes	Potato	Mixed Pickle
Maple Syrup	Corn	Cookies
Bread—Butter	Tapioca Pudding	Bread—Butter
Milk—Cream	Bread—Butter	Cocoa—Milk
Coffee—Cocoa	Milk	

Fifth Day

Breakfast	Dinner	Supper
Bananas	Soup	Lamb Stew
Pettijohns	Corned Beef	Vegetables
Codfish Cakes	Potato	Cinnamon Rolls
Rolls	Cabbage	Bread—Butter
Bread—Butter	Pie—Cheese	Cocoa—Milk
Milk—Cream	Bread—Butter	
Coffee—Cocoa	Milk	

Sixth Day

Stewed Figs	Soup	Macaroni—Cheese
Hominy	Fish	Layer Cake
Eggs	Potato	Pineapple
Bread—Butter	Tomatoes	Bread—Butter
Milk—Cream	Bread Pudding	Cocoa—Milk
Coffee—Cocoa	Bread—Butter	
	Milk	

Seventh Day

Rhubarb	Soup	Cold Ham
Oatmeal	Steak	Creamed Potato
French Toast	Potato	Lemon Jelly
Syrup	Lima Beans	Soda Biscuit
Bread—Butter	Baked Custard	Bread—Butter
Coffee—Cocoa	Bread—Butter	Cocoa—Milk
Milk—Cream	Milk	

A group of forty patients on varying grades of exercise, with a few "complete rest" cases, made satisfactory weight gains, and in other respects did well on this diet, averaging somewhat over 3,100 calories, with approximately 150 gm. protein.

In another division of Loomis Sanatorium (Intermediate Division) during the same period a more expensive diet was served—an example of which is given in the following list of menus for seven days. The actual consumption of food from this diet by a group of fourteen patients, equally divided as to sex, was somewhat less than in the former case; the results as to weight gains, etc., were about the same.

Intermediate Division Menus for One Week—Cost per Person per Diem, 40 Cents

First Day

Breakfast	Dinner	Supper
Grapefruit	Tomato Bisque	Cold Roast Beef
Farina	Roast Duck	Browned Potato
Omelet	Stuffing	Coconut Cake
Muffins	Gooseberry Jam	Bread—Butter
Butter	Creamed Onions	Cocoa—Tea
Coffee—Cocoa	Mashed Potato	Milk
Milk—Cream	Ice Cream	
	Bread—Butter	
	Milk	

Second Day

Breakfast	Dinner	Supper
Bananas	Bouillon	Roast-beef Hash
Oatmeal	Roast Spare Ribs	Chicken Salad
Boiled Eggs	Sauerkraut	Lemon Jelly
Rolls	Sweet Potato	Whipped Cream
Butter	Boiled Potato	Bread—Butter
Coffee—Cocoa	Plum Pudding	Cocoa—Tea
Milk—Cream	Brandy Sauce	Milk
	Milk	

Third Day

Oranges	Bean Purée	Lamb Chops
Wheatena	Roast Veal	Boiled Rice
Eggs	Potato	Plums
Potato Scones	Parsnips	Cake
Bread—Butter	Lettuce	Bread—Butter
Coffee—Cocoa	Pie	Tea—Cocoa
Milk—Cream	Bread—Butter	Milk—Cream
	Milk	

Fourth Day

Apricots	Vegetable Soup	Cold Ham
Saxon Wheat	Broiled Steak	Creamed Potato
Bacon	Tomatoes	Fruit Salad
Griddle Cakes	Potato	Boston Cookies
Syrup	Tapioca Pudding	Raspberries
Bread—Butter	Bread—Butter	Bread—Butter
Coffee—Cocoa	Milk	Cocoa—Tea
Milk—Cream		Milk

Fifth Day

Prunes	Soup	Lamb Stew
Pettijohns	Roast Beef	Biscuit
Eggs to order	Browned Potato	Peaches
Muffins	Beets	Cake
Bread—Butter	Steamed Pudding	Bread—Butter
Coffee—Cocoa	Foamy Sauce	Tea—Cocoa
Milk—Cream	Bread—Butter	Milk
	Milk	

Sixth Day

Oranges	Soup	Steak
Oatmeal	Fish	French-fried Potato
Codfish Cakes	Asparagus	Lettuce
Rolls	Potato	Pears
Butter	Rice Pudding	Cookies
Coffee—Cocoa	Bread—Butter	Bread—Butter
Milk—Cream	Milk	Cocoa—Milk

Seventh Day

Breakfast	Dinner	Supper
Bananas	Cream Soup	Cold Meat
Hominy	Roast Lamb	Macaroni
Bacon	Potato	Tomatoes
Corn Bread	Corn	Apple Sauce
Bread—Butter	Baked Custard	Layer Cake
Coffee—Cocoa	Caramel Sauce	Bread—Butter
Milk—Cream	Bread—Butter	Cocoa—Tea
	Milk	Milk

It will thus be seen that a well-balanced and efficient diet for the ordinary tuberculous patient may be constructed at a cost for raw food material of 30, or in some sections possibly as low as 25, cents per person per diem. It will be seen also that the cost increases rapidly as the diet becomes more elaborate, even without any increase in the nutrition value.

In institutions for paupers and incompetents, where actual physical disease has not to be considered, it is quite possible to furnish a ration which shall have the necessary calorific value and a sufficient protein content for as little as 15 or 16 cents per person per diem, and in several institutions of the sort such a low cost is actually maintained. But, while a diet so constructed may be practicable and efficient under such circumstances, it would be an extremely hazardous and unjustifiable experiment to attempt to reduce the cost of diet to any such figures in the case of tuberculous invalids in or out of institutions. Indeed, it would be of very doubtful expediency to attempt to reduce the cost in the latter case much below 30 or possibly, under some circumstances, 25 cents at the present price of foodstuffs (1911).

Diet in Far-advanced, Acute, and Complicated Cases.—During acute exacerbations arising in the course of an otherwise favorable case, such as may follow an "overdose" of exercise or tuberculin, there is no indication for any special change in the ordinary dietary, although the patient, being immobilized, that is, placed on "absolute rest" and during the period of fever, will naturally take less food owing to the incidental falling off in appetite. This need excite no apprehension, nor is it per se a condition calling for supplementary diets of eggs and milk. The patient will in fact do better if not disturbed by any departure from the food routine to which he has become accustomed.

But in cases of progressive disease and continued hyperpyrexia, or in the presence of certain complications, it will often become necessary to make more or less radical changes both in the constituency and the frequency of the diet, with a view of maintaining a sufficient nourishment. In "far-advanced" and progressive cases, where the patient has lost all appetite for regular meals, and has a repugnance for food as ordinarily served, it is wise to give small quantities at frequent intervals for such a period as conditions will determine. It is an excellent practice in such cases to divide the total amount of food to be given into eight parts, to be given at two-hour intervals through the day, the larger portions coming at the regular meal hours.

The following "two-hour" diet is one which has been found very serviceable in these cases in the hospital of Loomis Sanatorium. It affords a sufficient variety and total quantity in such small portions as not to excite repugnance even when there is a decided anorexia:

Regular Two-Hour Diet

	First Day			*Second Day*		
6.00 A. M.	Milk	6 oz.	= 170 gm.	Milk	6 oz.	= 170 gm.
	1 Raw Egg			1 Raw Egg		
8.00 A. M.	Orange	3 oz.	= 90 gm.	Grapes	3 oz.	= 90 gm.
	Oatmeal	3 oz.	= 90 gm.	Cream of Wheat	3 oz.	= 90 gm.
	Cream—Sugar			Cream—Sugar		
	2 Soft Cooked Eggs			Butter	½ oz.	= 14 gm.
				Bread	½ oz.	= 14 gm.
10.00 A. M.	Broth	4 oz.	= 120 gm.	Cocoa	3 oz.	= 90 gm.
	Toast	½ oz.	= 14 gm.	Toast	½ oz.	= 14 gm.
	Beef Juice	3 oz.	= 90 gm.	Beef Juice	3 oz.	= 90 gm.
12.00 M.	Soup	4 oz.	= 120 gm.	Cream Soup	4 oz.	= 120 gm.
	Chicken	1½ oz.	= 42 gm.	Lamb Chop	1½ oz.	= 42 gm.
	Potato	2 oz.	= 60 gm.	Potato	2 oz.	= 60 gm.
	Ice Cream	3 oz.	= 90 gm.	Bread—Butter		
2.00 P. M.	Hot Chocolate	4 oz.	= 120 gm.	Beef Juice	3 oz.	= 90 gm.
	Bread-Butter Sandwich	1 oz.	= 28 gm.	1 Raw Egg		
4.00 P. M.	Milk	6 oz.	= 170 gm.	Milk	6 oz.	= 170 gm.
	Beef Juice	3 oz.	= 90 gm.	1 Raw Egg		
6.00 P. M.	Broth	4 oz.	= 120 gm.	Beef Broth	4 oz.	= 120 gm.
	Stewed Fruit	2 oz.	= 60 gm.	Lettuce Salad	1 oz.	= 28 gm.
	Scraped Beef Sandwich—Beef —Bread	1 oz. ½ oz.	= 42 gm.	Toast	½ oz.	= 14 gm.
8.00 P. M. 10.00 P. M.	Milk	6 oz.	= 170 gm.	Milk	6 oz.	= 170 gm.

	Third Day	*Fourth Day*
6.00 A. M.	Milk .... 6 oz. = 170 gm. 1 Raw Egg	Milk .... 6 oz. = 170 gm. 1 Raw Egg
8.00 A. M.	Fruit .... 3 oz. = 90 gm. Bacon .... 1 oz. = 28 gm. Potato .... 1 oz. = 28 gm. Toast .... 1 oz. = 28 gm. Coffee	Fruit .... 3 oz. = 90 gm. Cocoa .... 4 oz. = 120 gm. Toast .... ½ oz. = 14 gm. 1 Raw Egg
10.00 A. M.	Shredded Wheat.. 1 = 35 gm. Cream .... 1½ oz. = 42 gm. Sugar 1 Raw Egg	Lettuce Sandwich Milk .... 6 oz. = 170 gm. Beef Juice .... 3 oz. = 90 gm. 1 Raw Egg
12.00 M.	Chicken Broth ... 4 oz. = 120 gm. Rice .... 1 oz. = 28 gm. Beef Sandwich	Thick Soup ..... 4 oz. = 120 gm. Chicken .... 1 oz. = 28 gm. Potato .... 1 oz. = 28 gm. Celery .... 1 oz. = 28 gm. Ice Cream .... 3 oz. = 90 gm.
2.00 P. M.	Egg Orangeade (1 albumin—1 orange) Beef Juice ...... 3 oz. = 90 gm.	Rice Pudding ... 2 oz. = 60 gm. Bread—Butter
4.00 P. M.	Milk .... 6 oz. = 170 gm. 1 Raw Egg	Milk .... 6 oz. = 170 gm. 1 Raw Egg
6.00 P. M.	Steak .... 2½ oz. = 75 gm. Potato .... 1 oz. = 28 gm. Baked Apple .... 3 oz. = 90 gm. Bread—Butter	Scraped Beef Sandwich Fruit Salad ..... 2½ oz. = 75 gm. Beef Juice ...... 3 oz. = 90 gm.
8.00 P. M. 10.00 P. M.	Milk.. 6 oz. = 170 gm.	Milk .... 6 oz. = 170 gm.

	Fifth Day	*Sixth Day*
6.00 A. M.	Milk .... 6 oz. = 170 gm. 1 Raw Egg	Milk .... 6 oz. = 170 gm. 1 Raw Egg
8.00 A. M.	Cream of Wheat.. 3 oz. = 90 gm. Cream—Sugar Toast Coffee	Fish .... 2 oz. = 60 gm. Toast Beef Juice Coffee
10.00 A. M.	Egg Lemonade Beef Juice	Cocoa 1 Raw Egg

	Fifth Day (continued)		*Sixth Day (continued)*	
12.00 M.	Soup	4 oz. = 120 gm.	Steak	2½ oz. = 75 gm.
	Scraped Beef Sandwich		Potato	
	Celery or Onion	1 oz. = 28 gm.	Custard	3 oz. = 90 gm.
			Milk	
2.00 P. M.	Broth	4 oz. = 120 gm.	Gruel	3 oz. = 90 gm.
	Bread—Butter			
4.00 P. M.	Milk		Milk	
	1 Raw Egg		Beef Juice	
6.00 P. M.	Cornmeal Mush	3 oz. = 90 gm.	Omelet	3 oz. = 90 gm.
	Cream—Sugar		Toast	1 oz. = 28 gm.
	Fruit	3 oz. = 60 gm.	Apple Sauce	3 oz. = 90 gm.
	Milk			
8.00 P.M. 10.00 P.M.	Milk	6 oz. = 170 gm.	Milk	6 oz. = 170 gm.

Seventh Day

6.00 A. M.	Milk	6 oz. = 170 gm.
	1 Raw Egg	
8.00 A. M.	Bacon	1 oz. = 28 gm.
	Toast	
	Coffee	
10.00 A. M.	Grape Nuts	2 oz. = 60 gm.
	Cream	
	1 Raw Egg	
12.00 M.	Roast Beef	2 oz. = 60 gm.
	Apple-nut Salad	2 oz. = 60 gm.
	Bread—Butter	
2.00 P. M.	Milk (4) Toast (1) oz.	
	Milk	
4.00 P. M.	Beef Juice	
	1 Raw Egg	
6.00 P. M.	Lamb Chop	1½ oz. = 42 gm.
	Potato	
	Junket	
	Toast	
	Beef Juice	
8.00 P. M. 10.00 P. M.	Milk	6 oz. = 170 gm.

This is a well-balanced ration averaging about 2,500 calories and, if well borne, will maintain nutrition or even effect weight gain in spite of high temperature and progressive disease.

It sometimes happens, however, that such a diet is not well borne, and appears to cause gastric and intestinal disturbance, or at least to cause in the patient a sense of discomfort. In such cases, or when there is reason to believe that the diet may be in part the cause of temperature, as imposing too great a strain on the digestive functions a semiliquid or, in extreme cases, a liquid diet may be substituted and often successfully. Following are examples of such diets which have been found in actual experience very satisfactory:

Two-Hour Semiliquid Diet

First Day

8.00 A. M.	Plums	
	Farina	4 oz. = 120 gm.
	Toast	1 oz. = 28 gm.
	Cocoa	4 oz. = 120 gm.
	Cream	4 oz. = 120 gm.
	Butter	½ oz. = 14 gm.
10.00 A.M.	Beef Juice	3 oz. = 90 gm.
12.00 M.	Cream of Pea Soup	
	Zwieback	1 oz. = 28 gm.
	Butter	
	Ice Cream	3 oz. = 90 gm.
	Milk	6 oz. = 170 gm.
2.00 P. M.	1 Raw Egg	
4.00 P. M.	Milk	6 oz. = 170 gm.
6.00 P. M.	Milk	6 oz. = 170 gm.
	Toast	1 oz. = 28 gm.
	Butter	½ oz. = 14 gm.
	Junket	3 oz. = 90 gm.
8.00 P. M.	Cocoa	5 oz. = 140 gm.
AVERAGE	Protein	120 gm.
	Fats	138 gm.
	Carbohydrates	225 gm.
	Calories	2,622

	Second Day	*Third Day*
8.00 A. M.	Oranges	Grapes
	Pettijohns	Oatmeal
	Toast	Toast
	Butter	Butter
	Cocoa	Cocoa
	Cream	Cream
10.00 A. M.	Beef Juice	Beef Juice
12.00 M.	Cream of Tomato	Cream of Spinach
	Zwieback	Zwieback
	Butter	Butter
	Charlotte Russe	Junket
	Milk	Milk
2.00 P. M.	1 Raw Egg	1 Raw Egg
4.00 P. M.	Milk	Milk

Second Day (continued)		*Third Day (continued)*
6.00 P. M.	Cocoa	Milk
	Toast	Rice
	Butter	Toast
	Custard	Butter
8.00 P. M.	Milk	Cocoa

Quantities for second and third days relatively the same as for first day.

2,000 CALORIES—LIQUID DIET

8.00 A. M.	Cocoa	1 cup (small)
	Eggs	2
	Milk	1 cup
	Orange Juice	(1)
10.00 A. M.	Eggnog	1 Egg 1 cup Milk
12.00 M.	Soup	1 cup
	Milk	1 cup
	Junket	4 oz. = 120 gm.
	Egg	1
2.00 P. M.	Cocoa	1 cup (small)
	Beef Juice	3 oz. = 90 gm.
4.00 P. M.	Milk	1 cup
	Egg	1
6.00 P. M.	Cocoa	1 cup (small)
	Milk	1 cup
	Eggs	2
8.00 P. M.	Hot Milk	1 cup
AVERAGE	Milk	48 oz. = 1,350 gm.
	Cocoa	13 oz. = 370 gm.
	Raw Eggs	7
	Soup	6 oz. = 170 gm.
	Beef Juice	3 oz. = 90 gm.
	Junket	4 oz. = 120 gm.
	Sugar	1 oz. in Cocoa
	Orange Juice	3 oz. = 90 gm.

These semiliquid and liquid diets will be found especially serviceable in certain laryngeal cases, characterized by more or less distressing dysphagia, although such cases sometimes have a greater tolerance for solids than liquids.

It is scarcely necessary to point out that the expense of such dietaries is considerable, not only because of the greater cost of material, but on account of the greatly increased service (nurse or dietitian) required.

Constipation and diarrhea, arising from various causes, are not uncommon in the course of chronic tuberculosis. When due to extensive tuberculous involvement of the intestines, little can be expected from any form of treatment, but in any case better results can be expected from suitable modification of the diet than from any other method.

An obstinate constipation is frequently corrected by a diet similar to the following:

Anticonstipation Diet

	First Day	*Second Day*	*Third Day*
7.00 A. M.			
	Orange Juice	Orange Juice	Orange Juice
Breakfast			
	Apples	Figs	Pears
	Oatmeal	Pettijohns	Shredded Wheat
	Cream	Cream	Cream
	Sugar	Sugar	Sugar
	Egg—1	Lamb Chops	Omelet
	Coffee	Coffee	Coffee
Dinner			
	Chicken	Roast Beef	Roast Lamb
	Celery	Cauliflower	Peas
	Asparagus	Spinach	Carrots
	Brown Bread	Rye Bread	Brown Bread
	Butter	Butter	Butter
4.00 P. M.			
	Buttermilk	Buttermilk	Buttermilk
Supper			
	Lamb Chops	Broiled Chicken	Fillet of Beef
	Salad	Salad (Tomato)	Salad
	Honey	Brown Bread	Rye Bread
	Graham Bread	Butter	Butter
	Butter	Stewed Prunes	Apple Sauce
8.00 P. M.			
	Stewed Fruit	Fruit	Fruit

In the case of diarrhea it is wise to concentrate the diet as much as possible. The following example of such a diet has proved very satisfactory in such cases and permits of sufficient variety to be acceptable to most patients over protracted periods:

Concentrated Diet

	First Day		*Second Day*	*Third Day*
Breakfast				
Hominy	3 oz. =	90 gm.	Same, but vary style of serving eggs.	
Cream	1 oz. =	28 gm.		
Sugar				
Eggs	2			
Cocoa	4 oz. =	120 gm.		
Toast	1 oz. =	28 gm.		
Butter	½ oz. =	14 gm.		

First Day (continued)		*Second Day (continued)*	*Third Day (continued)*
Dinner			
Roast Lamb	2 oz. = 60 gm.	Broiled Chicken	Roast Beef
Rice	5 oz. = 140 gm.	Baked Potato	Rice
Milk	1 cup	Milk	Zwieback
Zwieback	½ oz. = 14 gm.	Zwieback	Butter
Butter	½ oz. = 14 gm.	Butter	Milk
Supper			
Baked Potato	3 oz. = 90 gm.	Lamb Chops—2	Squab (or Chicken)
1 Egg (Omelet)		Rice	Baked Potato
Zwieback	½ oz. = 14 gm.	Zwieback	Zwieback
Butter	½ oz. = 14 gm.	Butter	Butter
Milk		Milk	Milk

Average	
Protein	110 gm.
Fats	115 gm.
Carbohydrates	260 gm.
Calories	2,500

Hyperchlorhydria is another condition arising frequently in certain stages of tuberculosis, to meet which an "anti-acid" diet is the most effective weapon available. Such a diet is the following, which is often sufficient to correct the trouble without other recourse:

		Anti-Acid Diet—Liberal		Anti-Acid Diet—Strict	
8.00 A. M.					
	Choice	Broiled Veal	70 gm.	Milk	200 gm.
		Stewed Veal	100 gm.	Soft Boiled Eggs	2
		Beef Steak	70 gm.	Toast	60 gm.
		Fowl	70 gm.	Butter	30 gm.
	Choice	Toast	30 gm.		
		Zwieback	20 gm.		
		Egg	1		
		Butter	20 gm.		
10.00 A. M.					
		Milk	500 c.c.	Egg	1
		Toast	40 gm.		
		Butter	20 gm.		
12.00 M.					
		French Soup with Yolk of Egg		Chicken or Broiled Meat	100 gm.
	Choice	Raw Meat—Beef Steak	200 gm.	Spinach or Asparagus	100 gm.
		Broiled or Boiled Fowl	140 gm.	Stale Bread	100 gm.
		Broiled or Boiled Fish	140 gm.	Butter	30 gm.
		Asparagus Heads	100 gm.		
		Toast	20 gm.		
		Omelet Soufflé	120 gm.		
		Butter	10 gm.		
		Black Coffee	Small cup		

	Anti-Acid Diet—Liberal (*continued*)		Anti-Acid Diet—Strict (*continued*)	
4.00 P. M.				
	Milk	250 c.c.	Milk	150 c.c.
	Zwieback	60 gm.	Crackers	50 gm.
	Butter	20 gm.	Butter	30 gm.
6.00 P. M.				
Choice	Cold Meat	70 gm.	Milk	100 gm.
	Meat Jelly	100 gm.	Butter	25 gm.
	Toast	20 gm.	Zwieback	20 gm.
	Swiss or Dutch Cheese	20 gm.	Soft Boiled Egg	1
	Butter	20 gm.		
Average			Average	
	Protein	98 gm.	Protein	88 gm.
	Fats	132 gm.	Fats	166 gm.
	Carbohydrates	269 gm.	Carbohydrates	215 gm.
	Calories	2,736	Calories	2,787

Other indications arise in the course of many cases of tuberculosis which demand special dietetic consideration, but, as a rule, they are not due to conditions peculiar to tuberculosis and will be treated in other portions of this work to which they more properly belong. Diabetes mellitus and other forms of glycosuria, for instance, are not infrequent complications in tuberculosis, which preëminently call for dietetic treatment.

The recent work of Schmidt has thrown new light upon certain intestinal conditions which occur more or less frequently in tuberculosis, though by no means peculiar to it, characterized on the one hand by excessive fermentation, and on the other by putrefaction, and attended in both cases by diarrhea, but indicating quite different dietetic procedures. In the former a restriction of the carbohydrate element and in the latter of the protein (especially of animal protein) in the diet is indicated.

There is a growing tendency to regard a suitable diet in tuberculosis as not differing essentially from that in health. In the absence of complications and among cases pursuing a favorable course such a view is probably correct, but in consideration of the character and especially the chronicity of the disease, with the emaciation which is commonly one of its most striking features, the physician is forced to direct his attention to the question of nourishment, and for this reason diet in tuberculosis must continue to hold a prominent place in the therapeutics of the disease.

As regards constant deviation from the normal in the gastro-intestinal system, in otherwise uncomplicated pulmonary tuberculosis, there are certain conditions which are met with so often as to suggest at least a definite relation to the disease. From a large number of examinations of stomach contents following test meals made at Loomis Sanatorium, the conclusions were reached that: (*a*) In the *active* "incipient" cases the total acidity and motility are increased. (*b*) In the *inactive* "incipient" stage there is shown no uniform disturbance in these factors, only such as is found in non-tuberculous cases. (*c*) In "moderately" and "far-advanced" cases, *active and inactive,* the tendency inclines to a lowered total acidity and motility, especially in the active stage. It will be seen, therefore, that in certain stages of the disease there are indications for special dietetic consideration which cannot wisely be neglected if the best results are to be expected.

OPEN AIR

Of the three fundamental principles of tuberculosis treatment, rest, food and open air, I have reserved open air to be considered last, not because it is the least important of the three, but as a protest against a tendency to put it first and to make it the chief consideration of treatment. This tendency would have it usurp the position that justly belongs to rest. If in treating a patient with active tuberculosis one had to choose between rest without open air and open air obtained only at the expense of exercise there could be no hesitation in making the selection. Fortunately such a choice need seldom be made. I do not wish to belittle the just value of open air in the treatment of tuberculosis for this value is very great. However, no further champion is needed to defend its position. Until very recently every author writing about the treatment of tuberculosis has dwelt chiefly and sometimes even exclusively upon the importance of open air. Since time immemorial the accepted treatment for tuberculosis has been change of climate. Sanatoriums were planned and presently constructed in great number chiefly to satisfy a demand for open air. Many ingenious devices have been suggested to bring open air to those unable to go in search of it. To physician and to patient alike open air has become the corner stone of tuberculosis treatment. However, it is only proper to point out that factors other than open air play a significant part in bestowing the benefits that are often ascribed to open air alone. Change of climate means as well change from accustomed surroundings and duties and usually a change towards lessening mental and physical strain. Sanatorium treatment is something more than life in the open. The very fact that open-air devices are invented chiefly for patients abed indicates the reliance put upon the influence of rest. Let us admit that it is futile to attempt a separate estimate of the value of each factor of a patient's life in contributing towards recovery from tuberculosis. It is the combined effect of all the factors judiciously mingled that gives the result. After all it is only of academic interest to discuss the relative position of open air in treatment. It is enough to realize that it is of such great importance that every patient with tuberculosis should receive all of it that he can get. I have said that the ideal treatment for tuberculosis in reference to rest is absolute and continuous rest, in reference to open air it is constant and continuous open air. Therefore, absolute rest constantly in the open air is the ideal desideratum. Any deviation from this ideal is a compromise to individual and social demands.

Every one has felt the exhilarating effects of fresh air. One experiences these delights almost daily upon stepping from a closed room into the open air. Yet the exact manner in which this pleasing change is wrought is not fully understood. For a long time it was thought that the lassitude, drowsiness, headache and malaise that come upon us in crowded, stuffy rooms were the symptoms of intoxication from breathing vitiated air, vitiated by oxygen deprivation or by some hypothetical poisonous exhalation from the body. Observation has shown conclusively that the oxygen and carbon dioxid balance in the air is only under unusual circumstances sufficiently disturbed to account for such symptoms and, while it has been impossible to demonstrate poisonous exhalations in rebreathed air, there is on the contrary valuable indirect evidence that points against their presence. I need only refer to the well-known experiments that have been frequently repeated. A man confined in a closed cabinet and forced to rebreath a small amount of air will soon experience depression, drowsiness, headache and malaise. These symptoms promptly disappear if the air in the cabinet without being changed is simply set in motion by an electric fan. If at the advent of symptoms the man is made to breathe fresh air from without the cabinet no relief will follow provided the air in the cabinet is allowed to remain at rest. When the man confined within the cabinet is obviously ill, a man stationed without may breathe only the air from the cabinet without experiencing any unpleasant symptoms. These experiments show plainly enough that the ill effects of stagnant air and the beneficial effects of fresh air depend little if at all upon the amount of oxygen that is available but chiefly, if not exclusively, upon the physical effects of atmosphere upon the body. The immediate effects involve chiefly the functions of the skin as a heat-regulating mechanism and subsequently the circulation and metabolism in general. Therefore the important feature about open air is not its chemical composition but its physical properties, its temperature, humidity and motion. The physician must appreciate the importance of these well-established facts to bring to tuberculous patients the full benefits of open air. If the benefits of open air are thought to come alone from its pureness then all of the advantages of living in the open may be forfeited. Open air and pure air are entirely different things and no perfection of artificial ventilation will ever make the terms synonymous. The notion that the benefits of fresh air reside in its pureness led to a number of false practical conclusions. To breathe fresh air, not to live in it, was considered the important thing. To meet this end window tents were devised into which patients stuck their heads while the body extended into the warm room. To have only as much as the head in the open air is better than to have none, but open windows are obviously to be preferred. Again since oxygen exchange goes on in the lungs it was thought that the direct contact with fresh air had peculiarly healing virtues in pulmonary tuberculosis. Since the benefit of living in the open resides solely in a tonic effect upon the whole body this benefit must be just as efficacious in tuberculous lesions elsewhere as in tuberculosis of the lungs. As a practical point this inference is missed if one is justified in judging from the general neglect of this beneficent measure in treating tuberculosis other than pulmonary.

That the effects of open air depend upon temperature, moisture and motion is a matter of daily experience if we but pause to note it. How oppressive and enervating are still, hot, humid days and after the discomfort of such days what a delightful relief comes with a grateful breeze! In temperate climates the spring and autumn months are the most refreshing and stimulating. They are not so cold that people close themselves up in houses and yet the cool crisp nights are generously stimulating after the balmy days that invite life in the open. In the hot summer months the fortunate seek relief from oppression by flight to the seashore and the mountains. When all is said such everyday considerations remain our best guide to a proper use of open air for the tuberculous.

Few questions relating to the treatment of tuberculosis have been more bitterly discussed than the question of climate. Even now there is no uniformity of opinion about its value. Evidently the problem is complicated and difficult to solve, else the large share of attention it has received would long ago have cleared away all uncertainty. From what we have said about the value of open air we should choose as an ideal climate one that is cold enough to be stimulating and yet not so cold as to make living out difficult or impossible; one with a large number of clear sunshiny days to invite life in the open air; one relatively dry with gentle breezes but no hard winds. To these requirements we should add the further desideratum of a considerable diurnal and seasonal change in conditions. The element of change is highly important. A perpetually ideal climate would lose all of its advantages in the depressing influence of its monotony. It has been pointed out that races living under surroundings subject to widely varying climatic conditions surpass mentally and physically the races living in an even, equable, unchanging climate. Whatever climate may have to do with such differences, it is certainly true that variations in climatic conditions have a favorable stimulating effect upon the individual. Part of this influence may be due to the constant activity of regulatory metabolic functions and part to the happy mental effect that change of every kind brings with it.

To those fortunate enough to be able to enjoy climatic conditions approaching the ideal, tuberculosis treatment may be made very pleasant. Whether, when we in this way make it more pleasant, we also make it more effective, is another matter. It has been customary for every one pretending to write authoritatively about the treatment of tuberculosis to discuss at length the advantages and disadvantages of various climates. I shall not follow this precedent because I believe entirely too much emphasis has been put upon it and I am convinced that more harm has been done by injudiciously prescribing climate than by entirely ignoring it. Only rarely does a choice of climate present itself as a perplexing problem to the physician. To my mind the matter is severely simple.

Experience has convinced me that in most instances at least the early part of treatment is carried out better away from home than at home. The benefit of change of residence depends upon many factors and among these climate, I believe, is relatively unimportant. A change of climate has a tremendously stimulating effect irrespective of the climate to which the change is made. Every one has experienced even in health such beneficial effects of change. No doubt these benefits are due largely to the mental effect of escape from accustomed routine and worry and care. To the tuberculous patient this benefit is further enhanced by an appropriate setting. The concern of rearranging household and business cares is thrown aside and when there are no longer hourly incidents to force them upon memory and attention they are more easily forgotten. Again, he has come to a place renowned for its many well and active ex-patients. Often some friend has encouraged him to trust the wisdom of his decision to go away by pointing to the happy results of similar treatment in his own robust person. Yet again, he is surrounded by many patients whose plight is similar to his own and courage is stimulated by the cheerfulness with which misfortune is sustained and hope aroused by the results of treatment he hears about and sees on all sides. And lastly, if he has been sent off wisely, he has fallen under the care of an experienced physician who knows how to treat the tuberculous and to choose skillfully the innumerable details that go to make such treatment successful.

It is this last consideration, the skill of the physician chosen to look after the patient, that I believe gives to climate its paramount value. It does so happen that certain resorts are preëminent in this respect and these resorts, though widely scattered throughout the country and subject to conspicuously differing climates, still can all point to results comparable one to another. An individual patient may do better at one resort than at another but this does not influence the general result. No one can boast for any climate that the results of treatment are there more uniformly successful, or more quickly attained, or more enduring than they are in another climate. As an example one would not select the Adirondack Mountains as possessing to any remarkable degree the enticing qualities of an ideal climate. On the contrary many of these qualities are absent and none but variety can be pointed to as conspicuously present. Still Saranac Lake is renowned as a tuberculosis resort and it has justly become a mecca for the tuberculous. This renown has not been won for it by the excellence of its climate but by the unusual excellence of its physicians, a school of physicians founded and nourished by the enthusiasm of Trudeau and still flourishing upon the noble traditions he left after him. If this school of physicians, personnel, traditions and appurtenances were transplanted to any other section of the country they would there treat tuberculosis just as successfully as they now do at Saranac Lake. The same might be said of Denver, of Colorado Springs, of Asheville, of Liberty and of other places too numerous to mention. The physicians at these various places make it their particular business to treat tuberculous patients and they therefore do it far more successfully than physicians who give it only occasional attention. In France superior sanatoriums for children have been built at the seashore and the results obtained are so excellent that the conclusion has been drawn that tuberculous children do particularly well in marine climates. This conclusion does undue deference to climate, since equally good results are obtained at equally well-managed institutions located elsewhere. If a physician decides to send a patient away from home the essential thing he must know about the climates under consideration is the capacity of the respective physicians who practice there. All else is of secondary importance and may be decided by convenience, the preference of the patient, the question of expense and other matters of expediency.

A question commonly asked by patients is whether recovery gained in one climate makes it dangerous to return later to another. It is a common belief that a patient who makes a good recovery at a high altitude cannot safely return to his home at sea level. I think this is an unwarranted belief. It arose from the well-established observation that many patients who improve away from home relapse shortly after they return and again take up their accustomed life. The cause of these regrettably frequent relapses is a complete change in the manner of living and not a change of climate. They occur as often in patients who have been treated near home as in patients who have gone to distant climates.

SPECIAL METHODS OF TREATMENT

Specific Therapy

Since the discovery of the tubercle bacillus numerous investigators have hoped to find a specific cure for tuberculosis. Many of the best investigative minds in medicine have lent their efforts to the solution of this problem. A vast amount of labor has been expended in a search that still remains fruitless and none of the discoveries so far made incline us to believe that such a remedy will be discovered in the near future. Indeed all that we know about the nature of tuberculous infection and the manner of its progress discourage such a belief. However, since the memorable announcement by Koch of the curative properties of tuberculin, many similarly premature announcements have fired us to hope that the longed-for cure has at last arrived. After a brief period of enthusiasm, disappointment has invariably followed. The prospects of a cure have nearly always centered about some modification of Koch's original method; indeed so numerous have these modifications become that at present one would find it difficult to propose one that had not already been tried. None of these has proved to be the long-sought cure but many still believe that the experience gained from these studies is not altogether fruitless in the field of tuberculosis therapy.

Attempts to convey immunity passively have completely failed. Even a casual acquaintance with the immunological features of tuberculous infection would lead one to anticipate such a complete failure. The method is now only of historical interest and I need but mention the enthusiastic but barren work of Marmorek and Maragliano.

Regarding the value of active immunization in treatment there is still no settled opinion. Since Koch's original contributions there have been succeeding waves of enthusiasm for this method of treatment and intervals during which it has been but lightly regarded. At the moment it is not prized very highly but there still are many who consider it a valuable adjunct to other methods of treatment. The method is spoken of inclusively as tuberculin treatment. To use tuberculin successfully or even safely requires considerable knowledge of its mode of action and few physicians not specially interested in the treatment of tuberculosis would be willing to devote the time and study necessary to acquire this knowledge. Nor do I believe they would be sufficiently rewarded to encourage them to do so. Tuberculin treatment had therefore best be left to the few sufficiently interested to master the subject. While I for one believe it has definite value in certain cases, this value is not great enough to balance the very real danger of irreparable harm if used by the uninformed or careless. However, whether a physician desires to use tuberculin or not, it is advisable that he know something about the claims made for it and something about the methods usually employed.

Results Obtained with Tuberculin Treatment

The evidence in favor of the value of tuberculin is voluminous and diverse, but unfortunately much of it is desultory. It is not a tempting task to review it in a systematic way. Most of the evidence upon analysis is reduced to impressions which, though of importance as bespeaking a good name for tuberculin, yet do not necessarily force conviction. There are inherent difficulties in statistical studies of tuberculosis that make it arduous to seek the evidence in that direction, and animal experiments have been far from satisfactory. It is impossible to consider in detail detached bits of evidence, so the published results will be taken up in groups with only a number of specific illustrations.

Animal Experiments.—We begin with animal experiments because, if there were satisfactory evidence in this direction, it would be the most conclusive obtainable and would make all further evidence superfluous. However, no such satisfactory evidence exists. Numerous authors have tested the value of tuberculin in the control of experimental infections in animals, and the consensus of opinion is that its influence is by no means striking. Almost constantly the treated animals live a short time longer than the untreated, but tuberculin has never stopped or even limited an established infection. More favorable claims than these have been asserted, but they have not stood the test of repetition. It is common to read in the literature that animals have been "immunized" with different varieties of tuberculin. Such statements are seldom accompanied by detailed protocols and do not bear a close scrutiny. Other observers never confirm the results. Indeed from Koch to the present day each inventor of a new kind of tuberculin cites animal experiments to sustain his claims to its superior virtues. These experiments are characterized usually by their small number, the paucity of detail with which they are reported, and a general indefiniteness of methods and results. Often the report consists merely of a statement. It is well to remember that real immunity or resistance to tuberculous infection has been obtained only with living tubercle bacilli. While it would be a great comfort to have tuberculin treatment established firmly upon an experimental basis, still the absence of conclusive results in animals does not settle the question of its value. Experimental infection in animals and acquired infection in man are different aspects of the disease, and the value of tuberculin must rest ultimately upon the clinical results of its administration.

Clinical Results—*Clinical Impressions.*—In speaking of the clinical results of tuberculin treatment, we shall refer temporarily only to pulmonary tuberculosis, since the evidence adduced pertains almost exclusively to this, the most widespread type of the infection. Later we shall offer the available evidence that concerns other forms of the disease. Regardless of Koch's injunction that tuberculin was to be used only in early and moderately advanced stages of pulmonary tuberculosis, the remedy after its introduction was applied recklessly in all stages of the disease. Naturally enough the majority of the patients were hopelessly advanced. As was then the custom, large doses were administered, and it is shocking to glance at the clinical charts preserved from these days. Patients racked by a long illness and consumed by the fever of rapidly advancing disease were obliged to endure daily violent chills and the distressing symptoms characteristic of a severe tuberculin reaction. The absolute failure of tuberculin under these conditions to accomplish the promised results led to a profound reversal of feeling. The disappointment was so keen and the memory remaining so bitter that the weight of more recent conservative work has failed to overbalance the repugnance left in the minds of many physicians. The doom of tuberculin was sealed by the statement of Virchow that anatomical studies forced him to the belief that tuberculin treatment occasioned a mobilization of tubercle bacilli and a spread of the disease.

Although the early tuberculin era ended in disaster, still the results obtained even at that time were not all unfavorable. A prominent clinician has written reminiscently of the immediate and permanent benefits of tuberculin treatment judged after the sobering interval of nineteen years. He was a physician at Davos, himself suffering from the disease, when the remedy was first introduced. Many observers felt that the downfall of tuberculin was occasioned by its indiscriminate and unreasoned application, and that perhaps a more cautious dosage would avoid the dangers while preserving the beneficial effects. As early as 1891 a number of prominent physicians advocated the administration of small amounts and a cautious increase in dosage. Upon this plan many clinicians continued to use tuberculin, convinced that they were getting good results. In 1901 Goetsch published the first summary of the results of the treatment by this method upon a relatively large number of patients. These results received the endorsement of Koch, and from the time of their publication dates the modern era of tuberculin treatment. Numerous approving reports followed, and tuberculin rapidly gained a sure foothold as a method of treatment of recognized value. In the face of this approval consistent opponents have held out and have exercised a rigid criticism of the evidence adduced in its favor. Enthusiasm has led many tuberculin champions to overstate its case and to draw unwarranted conclusions from ridiculously insufficient data. This censorship has been of the greatest value in forcing us to recognize the worthlessness of many of the statistics upon which the value of tuberculin has been based, and to search for more convincing evidence.

The mass of personal testimony in favor of tuberculin cannot be put lightly aside in forming an opinion. Many authors consider it alone sufficient to force conviction, and seek no further evidence. However, to my mind, it has importance only by virtue of its mass, for the opinions taken separately, while founded upon experience, nevertheless, are supported for the most part by scant data. The character of these data must now receive our attention.

Clinical Statistics.—All statistical studies of pulmonary tuberculosis are surrounded with difficulties, and these difficulties are well-nigh insurmountable in a statistical study of methods of treatment. This statement takes into account the fact that there is no treatment that will cure tuberculosis. Methods of treatment may have more or less value, but the proof of their value is difficult to obtain, and just how valuable a method is generally eludes satisfactory expression. The statistics of tuberculin treatment upon which great store has been set are often pitifully crude upon analysis. The difficulty arises from the fact that in a disease of such long duration and such protean clinical manifestation, improvement and retrogression occur spontaneously in such an unpredictable way that the effects of treatment are hard to gage. Standards of diagnosis are variable, and accurate classification for purposes of comparison is almost impossible.

Differences in diagnosis concern mainly early cases of pulmonary tuberculosis, but the moderately advanced group is to a limited extent involved. Too much emphasis has been put upon slight abnormalities in pulmonary physical signs in the diagnosis of pulmonary tuberculosis. Our studies have convinced us that many patients with quiescent lesions have been treated in sanatoriums and now figure as cures in sanatorium statistics. I make this statement with confidence, since I have myself been guilty of the error. Whether it is or is not advisable to treat such cases in sanatoriums is an open question, but that they should not be included in statistics of the results of treatment is obvious. That they enter as a serious disturbing factor in our estimate of the curability of pulmonary tuberculosis is certain. For example, C. Spengler, with bovine tuberculin, obtains 100 per cent cures in Stages 1 and 2 (Turban's classification), with bovine and human tuberculin in 99.7 per cent. Such figures are beneath comment. Indeed I believe the factor to be so seriously disturbing that I lay little weight upon statistics of the results of treatment in closed pulmonary tuberculosis. Deductions would be far more convincing if only cases with tubercle bacilli in the sputum were included in such statistics. True, to enforce this demand would exclude from consideration a very important group of cases, but if there is no other remedy the lesser evil is to be preferred.

The difficulties of classification reside chiefly in the lack of correspondence between the extent of the disease and the severity of symptoms. A patient with very few physical signs may have rapidly progressing disease, while one with extensive physical signs may be in good condition, have no symptoms, and remain well indefinitely. Until the past few years Turban's classification, based entirely upon the extent of pulmonary involvement, was the one in general use. More recently the National Association has proposed a schema which takes into account the physical signs and the symptoms. This classification has been universally adopted in this country. In Germany a similar plan is in use which, however, differs from ours in some details, chiefly in the restriction of the incipient group. Although valuable as uniform plans for grouping cases, still they are far from satisfactory for rigid comparison; indeed, inherent difficulties make it impossible to propose a perfectly satisfactory classification. For instance, our moderately advanced group embraces widely different cases. One just missing the incipient group stands far apart from one just short of the advanced group. To these unavoidable difficulties investigators have added by following their own individual classifications. Many others disregard all classification and group their material in one lump, thus making it impossible to compare their results with any other data.

Although the classification of cases of pulmonary tuberculosis is inadequate, an estimate of the results of treatment is still more unsatisfactory. Personal impressions play a large part in the estimate. In a disease that requires years to bring about healing it is difficult to measure the influence of treatment that lasts six months. Most statistics that bear upon tuberculin treatment use as their standard of comparison the condition of the patient when treatment is begun as contrasted with his condition at its termination. During this period, however, tuberculin rarely is the only factor to be taken into account. Usually there are concomitant changes in the patient's surroundings and mode of life that deserve equal emphasis. Leaving this consideration aside, there are still serious objections to the standard of comparison itself. Upon what shall the test of improvement rest? Changes in the physical signs are not a satisfactory measure of the patient's improvement. It is notorious how persistent physical signs are, even when general improvement is marked. Again, though considerable healing may have occurred, the signs may show no diminution in extent, while, on the other hand, an area may have become more seriously involved and the signs still remain unchanged. Added to this is the difficulty of appreciating slight changes in physical signs, when a record written months before is the only source of comparison. Obviously wide latitude is thus given to personal interpretation.

Nor are the symptoms a safer guide. In all sanatorium patients, except the hopelessly advanced, symptomatic cure is the rule. That such symptomatic cure is untrustworthy evidence of the permanent value of treatment is shown by following patients after discharge from sanatoriums. Unfortunately a large proportion soon relapses. From the condition on discharge one cannot predict which cases will relapse and which will permanently hold improvement.

These objections to tuberculosis statistics have been recognized by investigators who seek to put the value of tuberculin treatment upon a firm basis. Therefore they have sought more satisfactory standards of comparison, and recently have proposed these standards: (1) working ability; (2) the disappearance of tubercle bacilli from the sputum; (3) duration of life. All three of these standards possess obvious advantages over the condition of the patient on discharge. They are arranged in the inverse order of their importance. While the working ability of the patient or his relative earning capacity, which is often considered equivalent, is a rough estimate of his condition, still the objection may be urged that the working capacity as gaged and reported by the patient himself will be influenced by social conditions and the individual's temperament. The disappearance of tubercle bacilli from the sputum is an objective fact shorn of all personal misinterpretations. Besides, since only patients with tubercle bacilli in the sputum are admitted to the study, the diagnosis is assured in each case. The disappearance of tubercle bacilli is an important indication of improvement, and if, under one method of treatment, bacilli disappear more regularly and earlier than under another it is a reasonable conclusion to assume that the method with the larger proportion of disappearance has decided advantages. Lastly, most convincing of all are statistics of life duration. This is the final and absolute test of treatment. Unfortunately, such statistics are gathered with great difficulty, and many years must elapse before the results are available.

It is evident that for tuberculin statistics to be of value a number of rigid requirements must be followed. To equalize the personal factor the cases should be studied by one man, or at least in an institution with continuous and permanent traditions. To overcome the influence of spontaneous variation in the course of the disease, a large number of patients should be studied. Side by side with the group of tuberculin-treated patients an equally large group of patients as nearly similar as possible should be observed under identical conditions, save that tuberculin is withheld. As a method of evaluating the results of treatment, the disappearance of tubercle bacilli from the sputum, the working ability, and the duration of life are to be preferred to the condition of the patient on discharge.

Moeller reported the first large comparative study of tuberculin treatment. His report is from the Belzig sanatorium, and the results are as follows:

Comparative Study of Tuberculin Treatment (Belzig Sanatorium)

Stage, Turban	Number		Healed (Per Cent)		Arrested (Per Cent)		Improved (Per Cent)		Unimproved (Per Cent) or Failed	
	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.	Tr.	Untr.
1	134	281	51	32	37	51	10	16	1	1
2	105	290	18	3	44	27	32	59	6	11
3	90	362	0	0	41	6	36	31	23	63
Totals........	329	933	27	10	40	26	24	35	9	28

A desire to present the results of tuberculin treatment unembellished has drawn me unwillingly into this lengthy preamble. However, fairness demands some such consideration. It will be seen that in the light of this criticism many statistical studies to which undeserved esteem has clung dwindle into personal impressions. As personal impressions they retain their just value. I hasten to give a few of the more important statistical studies, believing that without further comment the reader will be able to attach to them their real worth. Some of these studies have more historical interest than intrinsic value. I state them briefly, and those sufficiently interested to wish details must consult the original publications.

Denys reports in great detail the results of treatment in 442 patients all with tubercle bacilli in the sputum. He contrasts with these 35 untreated patients. The statistics were gathered over a period of five years. Of the treated patients 193, or 43.6 per cent, were cured; 56, or 12.6 per cent, arrested; 36, or 8.1 per cent, much improved; 39, or 6.5 per cent, improved; 19, or 4.2 per cent, stationary; 9, or 2 per cent, worse, and 100, or 22.6 per cent, dead. Of the 35 patients who refused treatment 4, or 11.4 per cent, cured; 2, or 5.7 per cent, remained stationary; 5, or 14.2 per cent, were worse; and 24, or 68.5 per cent, were dead. Of the 442 cases treated with tuberculin 193, or 43.6 per cent, lost tubercle bacilli from the sputum.

Schnoller reports using Denys' tuberculin in 211 patients with the following results:

TUBERCULIN TREATMENT WITH DENYS' TREATMENT

Results	1st Stage	2d Stage	3d Stage	Total Per Cent
Probably cured	17	30	2	49 (23.2%)
Greatly improved ...	6	65	34	105 (49.8%)
Improved	2	19	11	32 (15.2%)
Total...........	25 (100%)	114 (94.2%)	47 (72.3%)	186 (88.2%)

Stationary, Stages II and III, 16 cases; worse, Stage III, 6 cases; dead, Stages II and III, 3 cases. Of 148 patients 44, or 29.7 per cent, lost tubercle bacilli from the sputum.

Turban treated 86 patients with tuberculin and contrasts them with 241 untreated patients. Permanent healing was obtained in 53 per cent of the former and 39 per cent of the latter.

Nagel reports a large number of cases from the sanatorium at Cottbus. It is pertinent to note that but 15 per cent of the patients had tubercle bacilli in the sputum. The study included patients in the sanatorium from 1900 to 1905. During the years 1900 and 1901 tuberculin was not used, and the results are contrasted with those of 1902 to 1905, when tuberculin was used.

> "Of 96 patients with tubercle bacilli in the sputum treated with tuberculin 48 per cent lost the bacilli. Of 65 patients with tubercle bacilli in the sputum not treated with tuberculin 20 per cent lost the bacilli."

RESULTS OF TUBERCULIN TREATMENT (COTTBUS SANATORIUM)

Result	Stage I		Stage II		Stage III	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
A	111 (227)*	53.2 (41.6)	0 (18)	0.0 (10.0)	0 (0)	0.0 (0.0)
BI	84 (278)	40.2 (50.3)	21 (109)	25.3 (60.2)	0 (5)	0.0 (10.4)
A BI	195 (505)	93.4 (91.3)	21 (127)	25.3 (70.2)	0 (5)	0.0 (10.4)
BII	7 (47)	3.3 (8.5)	28 (40)	33.7 (22.1)	2 (27)	28.6 (66.7)
A BI BII	202 (552)	96.7 (99.8)	49 (167)	59.0 (92.3)	2 (32)	28.6 (66.7)
C	7 (1)	3.3 (0.2)	34 (14)	41.0 (7.7)	5 (16)	71.4 (33.3)
Total	209 (553)	100	83 (181)		7 (48)	
	762		264		55	

* The figures in parenthesis represent the tuberculin-treated. A = Clinically healed. BI = Full working ability. BII = Partial working ability. C = No effect; worse.

Reliable statistics covering life duration are those published by Brown from Saranac. His comments are as follows:

"While the number of patients treated with tuberculin at the Adirondack Cottage Sanatorium has not been large, the care with which the patients have been followed renders the following results of interest. To allow of comparison, since the number in each group varied so much from year to year, it is necessary to reduce or increase the number of treated and untreated in each class each year to 100. This gives the following tables, expressed in percentages, in which are included the results on discharge and the ultimate results of 185 patients treated with and 864 treated without tuberculin who remained in the institution over ninety days and had tubercle bacilli in their sputum:

RESULTS ON DISCHARGE

Cases	With Tuberculin	Without Tuberculin
Incipient:		
Apparently cured	56	50
Disease arrested	34	38
Active	10	11
Moderately Advanced:		
Apparently cured	27	6
Disease arrested	55	51
Active	18	43

The ultimate results, expresesd in percentages of those living one to fifteen years after discharge, proper allowance being made for the varying numbers in each year and class, are as follows:

ULTIMATE RESULTS

Cases	With Tuberculin	Without Tuberculin
Incipient:		
Apparently cured	88	78
Disease arrested	77	78
Active	33	27
Moderately Advanced:		
Apparently cured	91	86
Disease arrested	48	45
Active	41	22

These statistics indicate that on discharge the incipient cases have done somewhat better than those receiving no tuberculin, while the moderately advanced cases show much better results. The ultimate results do not show such marked differences, but indicate that the treated, both incipient and moderately advanced, do better.

I now present the sputum statistics, figures which, from their objectivity and their almost indubitable meaning, are extremely valuable. They speak strongly for the healing effect of tuberculin.

Kremser chose 110 patients expectorating tubercle bacilli, treating 55 of them with tuberculin. The patients were not selected, but were placed in the groups alternately as they were admitted. Of those treated with tuberculin 22, or 41 per cent, lost the bacilli; of those treated without tuberculin only 16, or 29 per cent.

Phillips finds that in his Stage II cases 58 per cent of those treated with tuberculin, against 19 per cent of the untreated, were rid of bacilli in the sputum; and in the Stage III cases 31 per cent of the treated, as against only 7 per cent of the untreated.

Turban reports that of 86 open cases treated by tuberculin 47.7 per cent lost their bacilli; of 24 untreated only 27.4 per cent.

Brown reports from Saranac that in the incipient cases 67 per cent of the tuberculin patients were rid of bacilli; of the others 64 per cent. In the moderately advanced the figures are respectively 44 per cent and 24 per cent.

Bandelier reports 500 cases, of whom 202 had tubercle bacilli in the sputum. On discharge after an average treatment of five to six months, 129, or 64.9 per cent, had the sputum changed from positive to negative. Twelve were in Stage I; of those 100 per cent became negative. Of the 113 in Stage III, 50 per cent became negative. Bandelier challenges the production of similar results without tuberculin, and says they are unparalleled in the literature. These figures are remarkable, yet they are based on a respectable number—202 cases.

It is important to note that these percentages are closely paralleled by those of E. Löwenstein, who quotes the gratifying number of 682 open cases. No case is reported that did not reach the dose of 10 mg. O. T. Four sputum examinations were required to establish a case as negative. Under the tuberculin treatment 361 of the 682 cases finally showed negative sputum—a percentage of 53. Such a result, he maintains, cannot be obtained in any other way than by tuberculin. His analysis of the results of twenty years of hygienic-dietetic cure without tuberculin gives only 15 per cent of the discharged as having no bacilli in the sputum.

Bandelier has classified the 500 cases above referred to, containing 202 open cases, also from the point of view of working capacity. Compared with the sputum results, the figures are as follows:

Tuberculin Treatment Compared with Sputum Results

Results	Total		Stage I Per Cent	Stage II Per Cent	Stage III Per Cent
	Cases	Per Cent			
Complete earning capacity on discharge	500	69.8	90.4	80.7	32.8
Sputum changed from positive to negative	202	63.9	100.0	87.3	44.0

It is seen from the table that statistics based on the sputum becoming negative afford a real evidence of improvement, even when that is judged from the purely symptomatic side. The parallelism between the two sets of figures is close, and forms an additional argument for taking the bacillary content of the sputum as a statistical basis.

Thus far I have spoken only of the results of tuberculin treatment in pulmonary tuberculosis. Favorable reports of treatment in so-called surgical forms of the disease are no less numerous. However, the number of cases treated by any one observer is small, and as far as I know there are no large statistical studies of parallel groups of cases. However, I have already emphasized that such personal evidence, though not strictly objective, is still of value. External forms of tuberculosis are particularly favorable for estimating the effects of tuberculin, and I may say that many ophthalmologists, for instance, are among its most ardent advocates. I will not give the published results in detail. Space does not permit, and those interested may seek further information in the original articles.

This mass of evidence shows very strikingly what a large number of advocates tuberculin has, and the statistical studies will point, with whatever weight may be attached to them, toward its value. From a consideration of this evidence the following conclusions seem to be warranted: Tuberculin is not a cure for tuberculosis, else such a detailed consideration were unnecessary. However, in many instances it promotes healing, and recovery is more certain and more lasting than without it. Such a conservative estimate of its influence ranks tuberculin as a favorable factor in the management of the disease, a favorable factor as rest and diet and fresh air are favorable factors. This being its position, it behooves us to give it a wide application, but not to use it to the exclusion of other favorable factors. It should be employed in combination with these. It must be understood that tuberculin cannot replace fresh air or rest or diet in the treatment of tuberculous infections, and that we will do more harm than good if we make its use an excuse for relaxing our vigilance in respect to other important measures.

Selection of a Tuberculin Preparation

We may reasonably assume that the evidence adduced in the previous section has stimulated the interested physician to look further into the subject of tuberculin treatment, and perhaps has created the desire to test its value himself. If such be his intention his next step will be to choose the tuberculin he wishes to use. Unfortunately the beginner is at once bewildered and discouraged by the large number of preparations offered him to choose from. Each product has its champion who proclaims its virtues superior to those of other tuberculins, and urges in support of these claims theoretical considerations and clinical results. I hope that the remarks made upon clinical deductions in estimating the value of any treatment in tuberculous disease will encourage the physician to review the alleged results critically. In view of recent investigations the whole question, at first so complicated, has become severely simple. But before stating the nature and results of these investigations we must give a brief statement of the composition and preparation of some of the most important tuberculins.

All the tuberculins may be divided roughly into three groups: (1) those prepared from the culture media in which tubercle bacilli have grown; (2) those prepared from the tubercle bacilli themselves; (3) those prepared by various methods of extracting the tubercle bacilli.

I may say briefly that all varieties of tubercle bacilli have been used in preparing tuberculins: human type, virulent and avirulent; bovine type, virulent and avirulent; avian and piscian tubercle bacilli. Also that innumerable variations in culture media have been introduced. Only a few of the variations have acquired any permanent importance.

The principal members of Group 1 are these:

Koch's Original or Old Tuberculin: O. T.; Preparation.—A bouillon medium enriched with 5 per cent glycerin and slightly alkaline is inoculated with tubercle bacilli of the human type. In a broad flask this is allowed to incubate at body temperature for six to eight weeks, at the end of which time the bacilli have grown into a flat sheet covering the surface of the fluid. Moistened fragments of the growth may have reached the bottom of the flask or may still be suspended at various depths. The entire contents are then subjected to a current of steam over a water bath for the purpose of sterilization, and for concentration into one-tenth of the original volume. The glycerin, not evaporating, thus constitutes 50 per cent of the resulting mixture. At this stage the bacteria (which have now been killed) are removed by filtration through a Chamberlain filter. There results a clear brown fluid of a characteristic odor, which keeps indefinitely and is ready for use.

Denys' Bouillon Filtrate: B. F.; Preparation.—The culture is prepared as for making original tuberculin (O. T.). At the end of the required interval, however, the mixture is not heated or concentrated in any way, but is at once passed through a bacteria-proof porcelain filter. The residue is rejected. The filtrate, a clear fluid, is supposed to contain only the soluble secretions of the bacilli, plus the metabolized culture media, and without any further modification is ready for use.

Jochmann's Albumose-free Tuberculin: A. F.; Preparation.—Following the lead of Proskauer, Beck, and Fraenkel, Jochmann grew tubercle bacilli on a protein-free medium made of water, 1,000; asparagin, 8; ammonium lactate, 6; sodium chlorid, 5; glycerin, 40; neutral sodium phosphate, 2. From this culture fluid Jochmann prepares tuberculins which he deems less toxic, but therapeutically not more efficient than those tuberculins derived from the usual mediums. One of these is known as tuberculin A. F. (albumose-free). A. F., unlike O. T., is heated only to 37° C., and is concentrated to only 25 per cent of the original volume. Tuberkulin Hell is heated to 100° C. Jochmann's clinical work was done largely with A. F.

The principal member of Group 2 is:

Koch's Bacilli-emulsion: B. E.; Preparation.—This, as the name indicates, is an emulsion of tubercle bacilli. The culture is grown as for O. T. The bacilli are filtered off, ground, but not washed. One part of the pulverized material is emulsified in 100 parts of distilled water, and an equal volume of glycerin added, making 50 per cent glycerin emulsion, 1 c.c. of which contains the immunizing substance of 5 mg. of dried tubercle bacilli.

The principal members of Group 3 are:

Koch's Tuberculin-residue or New Tuberculin: T. R.; Preparation. Highly virulent cultures as young as possible are grown. After four to six weeks the bacilli are filtered off and dried in a vacuum. One gram of the dried tubercle bacilli is ground in an agate mortar until a sample shows no intact bacilli. To the pulverized mass is added 100 c.c. of distilled water, and the mixture is then centrifugalized. The clear fluid resulting from this centrifugalization is poured off and is known as Tuberculin Oberes (T. O.). It contains substances not precipitable by glycerin. The sediment deposited by centrifugalization is again dried, powdered, and again taken up by a small quantity of water. Centrifugalization is repeated and the previous cycle again gone through, until there is no sediment except that composed of gross, accidental particles. The fluids resulting from all the centrifugalizations, except the very first, are united, and should total not more than 100 c.c. This fluid is slightly opalescent and is precipitable by 50 per cent glycerin. To the opalescent fluid 20 per cent glycerin is added for preservation. The resulting suspension is known as T. R., and it should contain in each cubic centimeter 2 mg. of solids, representing 10 mg. of dried tubercle bacilli. From the mode of manufacture it was assumed that T. R. contains none of the secretions of the bacilli as does O. T., and that it does contain substances from the body of the bacilli, which O. T. speciously does not contain.

Beraneck's Tuberculin; Preparation.—In 1903 Beraneck announced a tuberculin for which he claims only minimal toxicity and a high content of specific substances. He cultivates the bacilli on a non-peptonized 5 per cent glycerin bouillon medium which is not neutralized. The filtrate from this culture is known as T. B., or toxin-bouillon. The residue is shaken for a long time at 60° to 70° C. with 1 per cent orthophosphoric acid. Equal volumes of the unheated toxin-bouillon and of the orthophosphoric acid extract of the bacillary bodies are united to form Beraneck's Tuberculin of a concentration known as H.

Von Ruck's Watery Extract; Preparation.—Concentrate a culture in vacuo at 55° C. to 1-10 volume. (This takes about a month.) Filter through paper, then through porcelain. Precipitate with an acid solution of sodic-iodid of bismuth. Filter and neutralize the acid solution. Filter again. Precipitate with absolute alcohol to make 90 per cent alcohol, and filter. Wash the precipitate with absolute alcohol. Dry the precipitate and make a 1 per cent aqueous solution. Filter. The last filtrate is von Ruck's tuberculin.

Landmann's Tuberculol; Preparation.—Landmann believed that in the process of heating O. T. to 100° C. substances are destroyed that at lower temperatures can be extracted. In order to obtain not only those extractives that cannot withstand heat, but also those that cannot be extracted without heat, he uses fractional extraction at various temperatures. He grows in bouillon a highly virulent strain of the human type of the tubercle bacillus. The bacilli are filtered off by filter-paper, fragmented, and the fatty components removed. Extraction at 40° C. then occurs by a glycerin-normal salt solution. After decantation the residue is again extracted at 50° C. and so up to 100° C. The united extracts are now concentrated in vacuo at 37° C. In order to make the aggregation of tuberculous toxins still more complete the concentrated culture fluid is now added to the combined extractives; and the entire amount is filtered through porcelain for sterilization. Finally ½ per cent phenol is added. The product is marketed by Merck as Tuberculol A.

It will be seen from the above list, incomplete though it is, that there has been a feverish strife to improve old tuberculins and to produce ever new and better tuberculins. Two considerations have prompted these efforts:

1. The attempt, under the assumption that they are many, to include all of the potent portions of the tubercle bacillus in the preparation.
2. The attempt to remove supposed deleterious substances from the culture media or the bacilli themselves, while preserving uninjured the beneficial or immunizing substances.

The first consideration was based upon principles of immunity established for other diseases and transferred without warrant to tuberculosis. As is well known, bacteriologists have distinguished two different poisonous substances obtained from bacteria: (1) exotoxins, or toxins secreted by the organisms and present in the culture media; and (2) endotoxins, or toxins intimately bound up with the living protoplasm of the bacteria and liberated only upon their disintegration.

Exotoxins are probably a product of bacterial metabolism, and their distinguishing features are their primary toxicity and the readiness with which they stimulate in the animal organism the production of neutralizing bodies called antitoxin.

Endotoxins are intimately bound up with the living protoplasm of bacteria, and are liberated when the organisms are disintegrated by certain ferment or lytic substances within the body. Although it is claimed that antitoxins to endotoxins have been obtained, their appearance is at least exceptional, and in general it is correct to say they produce no antitoxin.

Until recently it was customary to look upon tuberculous infections as producing specific secretions primarily toxic to the body. The symptoms of intoxication so common in the disease—fever, loss of weight, digestive disturbances, etc.—were looked upon as the direct effects of this toxin. To this toxin it was supposed the body reacted by the production of antitoxin, and the presence or absence of general symptoms depended upon the balance existing between the two. However, though the toxin might be completely neutralized and general symptoms be absent, still the tubercle bacilli in the tuberculous lesion might continue to live and, indeed, to multiply and to spread. The antitoxins therefore had no effect upon the bacteria. To inhibit their growth the body must elaborate antibacterial substances, the production of such substances being a response to the stimulation of the bacteria themselves. It was concluded that in order successfully to combat tuberculous infections we must stimulate the body artificially to produce both antitoxins and bacteriolysins. Since toxins are soluble they must, of course, be present in the culture media, and broth filtrates were used to produce antitoxins. The bacteria themselves must be injected if we hope to reach any degree of antibacterial immunity.

It was these considerations that led Koch to prepare his different tuberculins. In his earliest experiments Koch observed that subcutaneous inoculations of tubercle bacilli in tuberculous guinea pigs tended to prolong the life of the animals. However, necrosis and sloughing followed such inoculations, making the method impracticable for man. Following the established views of that day, Koch believed the healing effect of the injections to be due to diffusible substances, toxins secreted by the bacilli, and to avoid the necrosis used the broth filtrate instead of the bacilli themselves. Experience showing that, though the filtrate had a favorable influence upon the disease, still it did not satisfactorily control its progress, Koch once more turned to the bacillary bodies to obtain antibacterial immunity. The bacilli were ground up to prevent the occurrence of the necrosis that follows injections of whole organisms and the products called tuberculin-residue or T. R. and bacillen-emulsion or B. E. Furthermore, to obtain the full immunizing value of tuberculin he advised combining a filtrate and the bacillary body, for example, O. T. and B. E.

Such reasoning is not in accord with the latest views upon the nature of tuberculous infection and the mode of action of tuberculin. We know little directly about the endotoxins of tubercle bacilli, but nothing about the soluble toxins they are supposed to secrete. Indeed, all of the evidence we have accumulated about tuberculin goes to prove that the tubercle bacillus produces no true toxin. Single or repeated injections of large or small amounts of tuberculin never produce antitoxins in a healthy animal, nor do they cause antituberculin to appear in the blood.

We know too little about the constitution of tuberculin to identify it by any chemical test. There is only one characteristic of tuberculin that is absolutely specific, namely, its power to produce a certain reaction in tuberculous animals. The features of this reaction are well known, and will be considered in detail later. Briefly, they are redness and swelling at the point of injection, inflammatory reaction about the lesion, and fever and other constitutional symptoms. Recent investigations have shown conclusively that the potent substance in tuberculin, the substance that causes this reaction, is the protein of the tubercle bacillus. This protein produces qualitatively always an identical reaction, whether the culture fluid be used, the bacilli themselves, or the pure protein extracted from the bacilli. A product containing this protein is a tuberculin, and no substance that does not contain it can be so classified. There is no other characteristic mark of a tuberculin.

Wolff-Eisner has emphasized this point. He has worked with tuberculin which was shown microscopically to contain numerous acid-fast tubercle bacillus particles. Passed through a Chamberland or Berkefeld filter, the filtrate is found free from such particles, and still it produces reactions identical with, although weaker than, those of the original unfiltered product.

Tubercle bacillus protein being the potent constituent of tuberculin and, according to modern evidence, the only potent constituent, therefore any tuberculin that contains the specific protein is a satisfactory tuberculin to use. This at once settles the discussion about the value of the many different tuberculins. They are all satisfactory tuberculins if they contain tubercle bacillus protein, and the test of the presence of the protein is their ability to produce a tuberculin reaction. I emphasize this point since one reads constantly in the literature, and particularly in advertising literature, that this or that tuberculin is to be preferred because it has been rid of reaction-producing substances while the immunizing substances have been retained. According to our present views the reaction-producing and immunizing substances are one, and to free a tuberculin of its power to produce a reaction in the tuberculous is to rob it of the substance that gives it value in treatment. Other tuberculins are urged as superior upon the ground that they are primarily more highly toxic than other tuberculins. This is the sole argument in favor of, for instance, tuberculol. But it must be evident from what has gone before that this claim has no substantial value.

Many authors contend that the specific constituents of tuberculin are more potent when subjected to the least possible amount of manipulation. They object to heat particularly, fearing that high temperatures may destroy or injure some of the constituents. This consideration led Denys to substitute B. F. for O. T. The argument is reasonable, but it is purely hypothetical. There is no evidence to indicate that the action of B. F. is in any essential different from the action of O. T.

I have not the space to discuss the nature of the tuberculin reaction. It must suffice to say that in its broad features it is a hypersensitive reaction similar to the hypersensitive reaction to other foreign proteins. If this be so it is an advantage to have the protein as pure as possible and free from admixture of other proteins. For this reason Jochmann prepared his albumose-free tuberculin, growing tubercle bacilli upon medium free from protein.

Much emphasis has been put upon the source of the tubercle bacilli from which the tuberculin is prepared. It has been generally known that different strains of tubercle bacilli produce widely varying tuberculins. The variation is in the strength alone, the character of their effects being invariably the same. So much has been claimed for difference in diagnostic and therapeutic effect between tuberculin from human and tuberculin from bovine tubercle bacilli that it is of the greatest importance to emphasize that this statement applies with equal justice to products from these two sources. Römer, after an extensive investigation of the effects of tuberculin from human, bovine, and fowl tubercle bacilli upon animals (guinea pigs, cattle, chickens, and rabbits), infected with human, bovine, and fowl tubercle bacilli, concludes that there is no essential difference in the character of the effects the three produce. Indeed, human and bovine tuberculin are so identical in their action upon infected animals that we may neglect to ascertain their source. These results are fully sustained in a recent publication of Weber and Dieterlein. These authors tested the effect of human and bovine tuberculin upon tuberculous cattle and upon guinea pigs infected with human and bovine bacilli. While they find that even marked differences in potency may exist in tuberculins from different sources, the quality of the reaction is always the same.

I hope that I have made it clear that the selection of a tuberculin is a very simple matter, since practically all tuberculins contain tuberculoprotein and are therefore efficient. I hope that I have also shown that all alleged proofs of the superiority of one tuberculin over another are specious. Indeed, the one conclusion that may justly be drawn from the foregoing exposition is that the simplest tuberculins are to be preferred if only for economy. Upon theoretical grounds Jochmann's A. T. has some advantages, and for this reason is becoming popular. In practice, however, these advantages are unimportant. Because they are the simplest we advise a choice to be made between O. T., B. F., A. T., T. R., and B. E. However, it may be possible that although these tuberculins are essentially equivalent, still there may be minor differences that make the selection of one or another of them more desirable. For instance, it is claimed that reactions come more unexpectedly and are more prolonged when bacillary emulsions are used than in treatment with the filtrates. The explanation for this difference may be purely mechanical, since it is difficult to get uniform suspensions of tubercle bacilli or coarse particles of their ground-up bodies. Many authors claim that patients displaying unusual sensitiveness to one preparation will tolerate another satisfactorily.

In speaking of the results of tuberculin treatment no doubt it was noticed that I disregarded entirely the particular tuberculin that had been employed. The results reported were obtained with different tuberculins. Those that have been most frequently mentioned in the various reports are Koch's O. T., T. R., and B. E.; Beraneck's tuberculin, Denys' B. F., Jochmann's protein-free tuberculin and the bovine tuberculins. In order to see whether in the treatment of any one form of tuberculosis better results were obtained with a particular variety of tuberculin I tabulated for each organ the choice tuberculin as it seemed to each author. I found that for all the organs the list is practically the same. For example, in the literature on the treatment of glands one of the following tuberculins is regarded by some authors as the most suitable for the treatment of glandular tuberculosis: Koch's O. T., T. R., or B. E., Beraneck's tuberculin, Denys' B. F., Jochmann's protein-free tuberculin. Now and again some other tuberculin is mentioned, but the three tuberculins of Koch, Denys, and Beraneck, with recently the protein-free preparations, are by far the most used. However, the individual preferences of authors may differ. Frequently mention is made, as by Bandelier and Roepke, or by Jochmann, that good results were obtained with any of the above tuberculins. We cannot, from a review of the literature, see that there is at present any clinical basis for preferring any one of the principal tuberculins over another. Preferences are often based on a worker's long-continued use of a special brand, and his consequent unwillingness to change. However, some writers feel that there is a demonstrable difference in the action of some of the chief tuberculins. For example, although Bandelier and Roepke think them all therapeutically efficient, they believe that O. T. causes more inflammatory changes at the focus, and that B. E. is more apt to give fever reactions than local changes. But they prefer B. E. as an antipyretic over O. T. when fever is already present. Brown has also noticed fever reactions with B. E., unaccompanied by other symptoms. Kehl thinks O. T. an efficient antipyretic, while Neuman prefers T. R. or B. E., as does F. Krause. However, Denys' B. F. and Beraneck's tuberculin have strong defenders of their antipyretic action. Bandelier and Roepke think T. R. or B. E. produce more antibacterial immunity than O. T., and yet Goetsch had to change from T. R. to O. T. in order to cause the disappearance of the bacilli from the sputum. Work with agglutinins does not bring us any nearer to a reasonable choice, since the weight-relation of the various brands has been so often disregarded. As for the protein-free preparations, Jochmann well says that, while they are somewhat less apt to cause fever than the others, the therapeutic effect is about the same. In other words, while the tuberculins grown on protein media contain small amounts of non-specific pyrogenic substances, these are not enough to hinder the therapy, and, furthermore, only infrequently is the fever due to the non-specific, rather than to the specific, components.

Selection of Patients

The physician, assured of the value of tuberculin, and having chosen the preparation he wishes to use, will next look about among his patients for cases suitable for treatment.

Bearing upon the choice of patients, it is important to point out again that tuberculin is not an antitoxin, not a neutralizer of the poisons produced by the disease, nor a germicide directly killing the tubercle bacillus. Whatever differences may exist between opinions regarding the exact mode of action of tuberculin, all observers are agreed upon this much, namely, that tuberculin acts by stimulating the patient, stimulating him to elaborate protective substances, or to an inflammatory reaction about the area of infection. In a sense tuberculin is a tax upon the patient, a whip to his natural powers of protection. With this one point firmly fixed in mind the common sense of any shrewd physician will guide him in the choice of patients suitable for tuberculin treatment.

Patients with their reacting powers spent in a long fight with the disease, or overwhelmed by a severe or widespread infection, will not be benefited by tuberculin. We would more easily believe that the treatment under such conditions is harmful. A patient in good general condition with an extensive lesion is in better condition to profit by the treatment than one with a small lesion that is producing constitutional symptoms and progressive exhaustion. To apply this principle specifically we might elaborate it as follows:

1. The most suitable patients for treatment are those with small localized lesions that are not producing constitutional symptoms, namely, early pulmonary tuberculosis, tuberculosis of glands, bones, and so on. You will no doubt remark that it is a wise forethought to select for tuberculin treatment those patients who respond most readily to any form of treatment. But why should not tuberculin be most beneficial to those most easily benefited? It is in keeping with our estimate of tuberculin, not a cure, but a favorable factor. Besides, I hasten to add that, while tuberculin does most good to patients with circumscribed local lesions, its most striking effects are produced in patients with more extensive disease.

2. The most striking results of tuberculin treatment are seen in patients in good, or, at least, fair, general condition, with moderately or far-advanced lesions. Many of these patients have reaped a measure of improvement from the hygienic-dietetic treatment, but have then for months remained stationary, going neither forward nor backward. Tuberculin is often just the stimulation they need to start them upon a course of rapid improvement. Such instances are not isolated; every one who has used tuberculin can point to a number of them, patients whose rapid and prolonged or lasting improvement has been one of the keenest satisfactions of his medical work.

3. Entirely unsuitable for tuberculin treatment are patients exhausted by the disease or with an actively progressing infection. Advanced cases with fever and emaciation are to be excluded, likewise instances of acute disseminated tuberculosis. I feel that one must look with suspicion upon reports of tuberculous meningitis cured by tuberculin treatment.

4. Between the group of patients definitely suitable for tuberculin treatment and the group definitely unsuitable there is a large class of border-line cases. They are not hopelessly advanced, and still have symp-

toms that clinicians refer to as the symptoms of activity of the disease. No general rule can be laid down about such cases; some are certainly benefited by tuberculin, some apparently receive no benefit. When tuberculin is cautiously given it does no harm, and in many patients belonging to this border-line group it must be started tentatively with a readiness to discontinue or to push on according to the results obtained.

In my own experience I have not seen striking benefits from tuberculin administered to patients with fever. Many authors praise it extravagantly as an antipyretic, and I am willing to concede that my disappointment has been due in part to my work being largely with ambulant patients. When patients with fever fail to respond to prolonged rest in bed, in my experience they usually fail to respond to tuberculin. And in patients with fever, or with their nutrition below par, a preliminary course of rest and out-of-door treatment will pave the way for a more satisfactory tuberculin cure.

Our studies of tuberculin statistics, if they have not convinced us, have at least pointed definitely to the more lasting results in those treated with tuberculin in comparison with those not so treated. Tuberculin treatment will therefore find a large field of usefulness in patients who have lost their symptoms of the infection under a hygienic-dietetic or sanatorium régime, but still display evident signs of the tuberculous lesion. Generally employed in such cases we believe it will improve the ultimate results of sanatorium treatment.

Many observers claim that the results of tuberculin treatment in surgical tuberculosis are far superior to those obtained in pulmonary tuberculosis. While literally true, relative conditions are not taken into account in this statement. I have emphasized the influence of the general condition of the patient upon tuberculin treatment. Surgical tuberculosis is usually unaccompanied by constitutional symptoms, while such an association is the rule in pulmonary tuberculosis. Experience has convinced me that pulmonary tuberculosis is as promising a field for tuberculin treatment as other forms of the infection if the condition of the patient be considered.

General Principles of Tuberculin Treatment

The physician, having chosen the tuberculin preparation he will use, and having selected a number of suitable patients, must have further a specific plan of action before beginning the treatment. He must have in mind very clearly just what he wishes to do. With this purpose firmly fixed he can easily avoid the difficulties and uncertainties that beset him.

Although there are innumerable variations in the methods of administering tuberculin, still, in a general way, these methods may be reduced to two: (1) the method of giving small doses and repeating the same small dose at stated intervals; (2) the method of starting with small doses and progressively increasing the dose, varying the time interval and rate of progression to suit individual conditions.

Method of Continuous Minimal Dosage.—The method of continuous minimal dosage was devised by Wright, and has received its main support from him and his school. Wright's contentions are based entirely upon his views regarding phagocytosis. As is well known he has demonstrated that the blood serum normally possesses the property of preparing foreign material for the phagocytic action of leukocytes. The substance in the serum that gives it this property he names opsonin. He has devised an ingenious method for estimating the opsonic power of serum, the resultant being termed opsonic index. The opsonic index toward different bacteria is regarded as specific. It varies in different individuals under influences that are not altogether understood. However, the main influencing factor is contact with the particular organism under consideration. When infection occurs the first movement of the opsonic index is downward (negative phase), followed, if the individual responds satisfactorily, by a rapid rise above the previous level (positive phase). In the fluctuations of the opsonic index Wright sees a valuable control of the response of the individual to the infection. Fluctuations similar to those occurring in natural infections may be brought about by the injection of vaccines prepared from the organisms. The variations of the opsonic index following such injections determine the size and interval of the dose.

These principles applied to a study of tuberculous infection led Wright to advocate for treatment small doses of T. R. given at intervals of from seven to ten days. The final test of the efficacy of a dose is the determination of the degree of opsonic response. But many such estimations have led to the adoption of a dose between 0.05 c.mm. and 0.001 c.mm. as generally applicable, and ten days as the best general interval.

Wright's work is to be welcomed as an attempt to put tuberculin treatment upon a sound experimental basis. However, the results of subsequent investigations have shown that the method of determining the opsonic index is far from accurate, and that the range of error is so wide that no legitimate inferences can be drawn from slight variations. Besides, we would scarcely be justified in using a single immunity reaction as a gage of the total reaction to an infection. Such a conclusion would follow only if extensive investigation established a constant relation between the two, and no such relation has been established for the opsonic index in tuberculous disease. It is true that Wright regards opsonic power as a by-product of antibodies possessing other functions and therefore a convenient indication of the amount of general antibody formation in the body. However, this view is not firmly grounded.

Indeed our knowledge of the relation of so-called antibodies to the degree of immunity and the intensity and course of the infection is very meager. In many clinical discussions of tuberculosis the word "antibodies" is used so confidently and so promiscuously that one is led to believe that this charmed word contains closed within its ten brief symbols all that mortal ever has learned or ever can learn of the disease. It explains infection and resistance; when it is whispered the veil that has so long hung before the tuberculin reaction falls away; a little more or a little less decides why we have tuberculosis and how we get well of it. Briefly, in some circles, every question that may be put about the infection is satisfactorily answered by this mystic symbol. That it is a convenient term and has a genuine significance based upon experimental data is true, but it loses all sense and dignity when, detached from this support, it is bantered about as the open sesame to the knowledge of infections.

I have already spoken of the contradictory evidence pertaining to the occurrence of complement-absorbing bodies in the serum. Agglutinins and precipitins bear no constant relation to the course of the disease. As has been said, no antitoxin in the sense of a substance capable of neutralizing tuberculin has ever been demonstrated.

Römer has applied the methods of demonstrating the various immune antibodies to the serum of his animals of proved strong resistance to reinfection, and has found none to correspond regularly with the degree of immunity. Agglutinins are almost constantly present, but may not exceed the amount present in normal animals. Immune animals may fail to show complement-absorbing antibodies, while the serum of others completely inhibits hemolysis. He was unable to demonstrate antitoxin in the sense of a substance capable of neutralizing tuberculin. The serum of immune sheep has no influence upon tubercle bacilli allowed to remain a long time in contact with it. It is not possible passively to transfer immunity through the serum from a tuberculous to a non-infected animal.

For a long time the method of giving small doses continuously drew support from considerations flowing out of our knowledge of anaphylaxis or hypersensitiveness. To make the matter clear we must go back to the original experiments of Koch. He tells in a very graphic way how he came to hit upon the use of tuberculin in treatment.

> "When one inoculates a healthy guinea pig with a pure culture of tubercle bacilli the wound as a rule closes and in the first few days seems to heal. However, in from ten to fourteen days a hard nodule appears, which soon breaks down, leaving an ulcer that persists to the time of death of the animal. There is quite a different sequence of events when a tuberculous guinea pig is inoculated. In tuberculous animals the inoculation wound likewise promptly unites. However, no nodule forms, but on the next or second day after a peculiar change occurs. The point of inoculation and the tissues about, over an area of from 0.1 to 1 cm. in diameter,

grow hard and take on a dark discoloration. Observations on subsequent days make it more and more apparent that the altered skin is necrotic. It is finally cast off and a shallow ulceration remains which usually heals quickly and permanently without the neighboring lymph glands becoming infected."

Healthy animals, then, react in a very different way from tuberculous animals to inoculations of tubercle bacilli. Extending Koch's early experiments it has been shown that tuberculous animals react in one of three ways to inoculation of tubercle bacilli:

1. If a large number of tubercle bacilli are injected the animal dies in a few hours with symptoms of a profound intoxication.
2. If the dose be small there is a prompt reaction about the site of injection which destroys the tubercle bacilli and prevents infection even of the regional lymph glands.
3. If the size of the dose be larger than that which the animal is able to resist, but not large enough to liberate acute fatal intoxication, infection does occur, but the resulting lesions are chronic and slowly progressing as compared with those produced by the same dose in normal controls.

Therefore, animals with tuberculosis can resist successfully reinoculation of tubercle bacilli in quantities surely fatal for normal animals, although the same mechanism which protects under these conditions is destructive when the number of bacilli is very large. The acute death following large doses has been studied in detail by Bail, the immunity to small doses most thoroughly by Römer. These results, so contradictory at first sight, are easily reconcilable. It is reasonably probable that the mechanism, whatever it may be, which causes the immediate toxic reaction on reinfection is the same as that upon which the animal withstanding this reinfection depends for its complete protection. How analogous these phenomena are to the general principles of anaphylaxis is at once apparent. The animals have by one infection been rendered hypersensitive to subsequent contact. This hypersensitiveness is, as we have shown, a valuable protective asset, but if the reinfecting dose be large the animal succumbs with the symptoms of an acute intoxication.

Von Behring, Koch, and Heymans have shown that calves may be protected against many times the fatal dose of bovine tubercle bacilli by injections of living human tubercle bacilli. Following this immunizing injection calves do not develop gross tuberculous lesions, but do acquire tuberculin hypersensitiveness; that is, they react to subcutaneous injections of tuberculin just as tuberculous animals do. After about a year tuberculin hypersensitiveness is lost, and as it dies out the animals again become susceptible to inoculation with bovine tubercle bacilli.

Resistance to tuberculous infection can be conferred artificially only by the introduction of living tubercle bacilli, and Trudeau has shown that the more virulent the organism the greater the protection. According to Römer tuberculin hypersensitiveness runs remarkably parallel with the intensity of experimental infections.

These results indicate that a close relation exists between protection against tuberculous infection and hypersensitiveness to tuberculoprotein, although we cannot say definitely that the hypersensitiveness and the protecting mechanism are the same. Indeed, Krause and Austrian have found that animals made hypersensitive by the injection of pure tuberculoprotein are more susceptible to infection than normal animals.

These experimental results have been applied to clinical conditions in man and emphasized chiefly by Römer, Hamburger, and Wolff-Eisner. They regard tuberculin hypersensitiveness, or the mechanism of which it is an expression, as a valuable asset in the fight against tuberculous disease. The question has been discussed interestingly by Baldwin. Wolff-Eisner views with alarm any measures taken to diminish hypersensitiveness. As is well known, tuberculin hypersensitiveness is influenced in a limited way by tuberculin injections, rapidly increasing doses diminishing it, small, frequently repeated doses increasing it. Therefore he considers the latter method more desirable for treatment. As clinical evidence to support this view Hamburger points to the marked resistance that tuberculous individuals have to reinfection, and Wolff-Eisner attempts to establish a relation between the degree of hypersensitiveness and the severity of the infection. He ascribes important prognostic significance to the tuberculin reactions.

To summarize briefly the conclusions that seem justified from the work on tuberculin hypersensitiveness in relation to tuberculous infections: Animals with tuberculous disease have a strong resistance against reinfections with tubercle bacilli. They withstand many times the fatal dose, but when very large amounts are given they succumb with stormy symptoms of an acute intoxication.

Although the animals are highly resistant to reinfection, this reinfection does not localize or overcome the original infection. Unquestionably it modifies its course, but I wish to emphasize that the mechanism is protective, not curative.

The parallel course of this resistance to superinfection and tuberculin hypersensitiveness is so striking that we are inclined to attribute both phenomena to the same mechanism.

I have frequently spoken of tuberculin hypersensitiveness as hypersensitiveness to tuberculoprotein. This is true in a general way, but all of the characteristics of the tuberculin reaction have not been reproduced experimentally with pure tuberculoprotein. Perhaps the difference is quantitative, not qualitative. Immunity is conferred only by inoculation of living tubercle bacilli, and immunity and the development of all the characteristics of tuberculin hypersensitiveness (for example, cutaneous hypersensitiveness) seem to depend upon tubercle formation, at least as far as we know they fail to occur unless tuberculous tissue is formed.

In spite of the close relation between tuberculin hypersensitiveness and resistance to reinfection, Römer is unwilling to identify the tuberculin reaction with the hypersensitive reaction following reinoculation. The former may be absent in animals which show a marked reaction to new infection and, as he points out, animals acquire tuberculin hypersensitiveness following the injection of dead tubercle bacilli, though they develop no resistance against infection.

I have written at such length of the experimental work on hypersensitiveness because it has completely modified our views of infection and the course of the disease in man. Though the field is tempting I cannot enter it, and must hurry to the relation of hypersensitiveness to tuberculin treatment. What I wish especially to call attention to is the double-edged character of the weapon. It cuts in two ways, for while it protects against reinfection and modifies the course of the disease, it is likewise responsible for the constitutional symptoms that accompany the infection. Thus, if the infected organism be exhausted by overstimulation it pays too dearly for the protection. Vaughan has put this in a striking way when he speaks of the anaphylactic shock as death from overprotection. Even though death may not occur, wasting and the other symptoms of intoxication are as much phenomena of hypersensitiveness as the protection against reinfection. To persuade these hypersensitive phenomena to subside is the aim of rest and the other well-established principles of tuberculosis treatment, and, unless the symptoms be severe, tuberculin in increasing doses is an important aid to this end. As tuberculin tolerance is acquired there follows usually a noteworthy change in the condition of the patient. The appetite and digestion improve, energy and vigor increase, and nervous symptoms abate. It is significant that with returning hypersensitiveness the usual symptoms of the disease again become prominent, to subside once more when tuberculin tolerance is reëstablished; that when relapse occurs hypersensitiveness reappears; and that as a general rule in manifest tuberculous disease, when it is impossible to overcome the patient's hypersensitiveness and procure even a moderate measure of tolerance for tuberculin, improvement in the general and local conditions does not occur.

I have so far been unable to confirm Wolff-Eisner's contention of the prognostic value of hypersensitiveness. Our work with tuberculin in diagnosis and treatment has led us to believe that tuberculin hypersensitiveness in relation to tuberculous disease runs, roughly, somewhat as follows: Since nearly all adults are infected with tuberculosis, we assume a low grade of tuberculin hypersensitiveness to begin with. Should there be a fresh invasion of the body from within or from without the tuberculin hypersensitiveness rapidly rises. If the disease subsides and the individual recovers the hypersensitiveness gradually falls to a lower level; if the disease remains active the high level of hypersensitiveness persists and lasts until the body is overwhelmed and its resistance broken down completely by the disease when hypersensitiveness disappears. Therefore, while we allow that in rapidly advancing cases the absence of tuberculin hypersensitiveness is an ominous sign in early and moderately advanced cases, we consider a low grade of hypersensitiveness a more favorable indication than a high. The high level hypersensitiveness rebellious to tuberculin treatment we have found to be of particularly unfavorable prognostic import.

It is still an open question whether tuberculin immunity or the loss of hypersensitiveness following the injection of increasing doses of tuberculin is identical with the loss of tuberculin reactivity that occurs in rapidly advancing tuberculous disease or during the course of other diseases, notably measles. The question cannot be answered until the fundamental mechanism of hypersensitiveness is better understood. My own impression from clinical observations is that the two cannot be the same. The loss of reactivity at the end of the disease is certainly an exhaustion phenomenon, while the loss following tuberculin treatment is certainly not due to exhaustion. The remarkable improvement in general condition so commonly accompanying tuberculin treatment makes such an explanation unreasonable. To Wolff-Eisner's contention that a high grade of tuberculin tolerance induced artificially will expose the patient to an acute exacerbation of the disease, I may reply, upon the experience of innumerable clinicians, that the fear is groundless. True it is that tuberculin immunity cannot be identified with tuberculosis immunity. Tuberculous complications and relapses occur in patients with a very high degree of tuberculin tolerance, but they do not occur more frequently than they do in untreated, highly hypersensitive patients. Indeed, clinical experience indicates that they occur less frequently.

The final and most cogent argument against the method of administering small doses without progression is that the plan has found little favor with clinicians. Although largely tried it has been generally abandoned. All are on the outlook for experimental data that will guide us in tuberculin treatment. We recognize that our methods are empirical, but until experiments are more clearly pertinent clinical evidence must have its weight.

Method of Increasing Dosage.—The method of tuberculin treatment that is most widely adopted and has behind it the force of accumulated clinical experience is the method of increasing dosage. It is true that there is a wide difference of opinion upon the details of the treatment, but the principles are fairly uniform.

There are two ways in which tuberculin may have a beneficial effect:

1. By stimulation or modification of the machinery of immunization, thus rendering the individual more resistant to the effect of the infection and aiding to limit the activity of the tubercle bacillus.

2. By direct stimulation of the focus of infection, thus promoting healing and, through the inflammatory reaction occasioned about the focus, bathing it more lavishly with the products of immunization.

I have already considered in some detail the first of these effects. Experimental evidence in regard to the relation of immunity reactions to infection and the progress of the disease is inconclusive. Agglutinins, precipitins, and opsonins are formed, but their rôle is not clear. About hypersensitiveness and its significance we are far better informed. But many details await further investigation. However, although we cannot fully explain its mode of action, still it cannot be doubted that tuberculin has a profound effect upon the condition of the patient. Its effect upon the symptoms spoken of as toxic I have repeatedly indicated, and indeed this effect is clinically so striking that naturally enough clinicians looked upon tuberculin as a primary toxin and tuberculin treatment as antitoxin stimulation. I have pointed out that this view is no longer tenable, but the observations upon which the view was based are too firmly established to be disregarded. To these observations we owe such current terms as tuberculin immunity (Trudeau) and *giftfestigkeit* (Sahli). Indeed, many experienced observers, notably Sahli and Denys, see in this so-called antitoxic effect the full value of tuberculin treatment.

It will be remembered that Koch considered the tuberculin reaction a necessary part of tuberculin treatment, feeling that the full effects of treatment were not obtained unless reactions occurred. In later publications he has never completely relinquished the idea of their importance. It is needless to review the experience of the first tuberculin era which was guided by this concept. There is no one point of tuberculin treatment upon which there is such general accord as the harmfulness of severe and, particularly, repeated severe general reactions. After repeated reactions patients almost invariably have a prolonged and tedious convalescence.

Although there is this general condemnation of severe reactions, still in milder form their effects may be beneficial. When tuberculous lesions are situated externally and are thus accessible to inspection slight focal reactions are often observed unaccompanied by constitutional symptoms. The view is rapidly gaining ground that such gentle stimulation frequently repeated encourages healing. No doubt these mild focal reactions constantly occur during tuberculin treatment. We do not know all the details of the relation between focal reactions and constitutional symptoms, but evidence points to a close relation. Indeed, many authors regard the symptoms of a tuberculin reaction as secondary to and dependent upon the focal reaction.

I must allow that we can draw no sharp line between the mild focal stimulation that we look upon as beneficial and the severe reactions that we regard with alarm. Every one who has had experience with tuberculin has seen occasionally marked improvement follow so directly upon a tuberculin reaction that he has been forced to ascribe a beneficial influence to it. I have already commented upon the favorable effect of Koch's violent methods upon some individuals. Again, some patients improve markedly in spite of, and I believe on account of, repeated mild constitutional reactions.

I have said that there is a wide difference of opinion about the details of conducting tuberculin treatment according to the method of slowly progressing dosage. However, for purposes of discussion it is convenient to divide the difference into two groups, accepting as the type of each the extreme opinions, while stating that most observers take an intermediate position.

The first group is represented by Löwenstein, Petruschky, Bauer and Engel, and others. The object of this plan is to reach high doses of tuberculin in the shortest possible time. Minor details of treatment are held subservient to this prime object. They begin by giving diagnostic doses of tuberculin to find to what amount the patient will give a general reaction. This initial dose having been determined, after a rest of from ten to fourteen days, treatment proper is begun with its repetition, or even with a dose a little higher. From this point on the dose is progressively and rapidly raised. If reactions occur the dose is repeated if necessary three or four times, and then again increased. Slight reactions are not held to be contra-indications for enlarging the amounts. Above all, the dose must never be decreased for fear of stimulating hypersensitiveness and making further advance impossible.

The second group is represented notably by Trudeau, Sahli, and Denys. While the aim is to arrive at as high a grade of tuberculin tolerance as possible, the reaching of high doses is not the ultimate object. Each patient is carried as high as his own individual tolerance will permit, and is never forced onward through reactions. Treatment is begun with doses so small that no reaction will be produced, and then cautiously raised, the slightest evidence of approaching sensitiveness being watched for. When these occur the amount of tuberculin is reduced, or at least held at the same level, until the indications have completely disappeared. The essential feature of the plan then is to avoid the slightest reaction, and, instead of attempting to reach an absolute high dose of tuberculin, to carry each patient to the measure of his individual tolerance.

It is at once apparent that which method we accept will depend entirely upon our attitude toward reactions. I am becoming more and more convinced that focal stimulation is the most potent factor in tuberculin treatment, but I am equally convinced that general reactions are often harmful. The contention of Sahli and other adherents of the gentle method of procedure is not that mild reactions do harm, but that, having no means of controlling their extent, there is constant danger of their surging out of bounds if we set about purposely to produce them. He feels that our first duty is to do no harm. I agree with Sahli that we succeed in reaching as high doses by the mild as by the more daring plan, that improvement is equally satisfactory and that less danger is run. On several occasions I have abandoned this conservative plan and used tuberculin more vigorously, but each attempt was followed by numerous general reactions. My experience has been gained almost entirely upon ambulant patients. It is possible that under institutional care and supervision a more rapid increase in dosage can be successfully followed.

The keynote, then, to tuberculin treatment is to hit the happy medium between sufficient and not too much focal stimulation. If we are to err it is safer to err on the side of too little than on the side of too much, but too timid a procedure will not give the full benefit of tuberculin, whereas an occasional mild constitutional reaction will do no harm. We believe that by careful observation one can give the proper amount of tuberculin and at the same time avoid objectionable reactions.

To put the conclusion of this important section briefly, the best method of using tuberculin in treatment is to give increasing doses with the purpose of producing the greatest amount of focal stimulation without liberating general reactions.

Preparation of Tuberculin Dilutions and Methods of Administration

For practical purposes we have found that the simplest method is to prepare a series of dilutions, each being one-tenth the volume strength of the former. Bottle No. 1 contains pure tuberculin; No. 2, 9 c.c. diluent and 1 c.c. tuberculin; No. 3, 9 c.c. diluent and 1 c.c. of 2; No. 4, 9 c.c. diluent and 1 c.c. of No. 3, etc. The diluent is 0.8 per cent salt solution with 0.25 per cent carbolic acid. To administer 1 c.mm. we would give 0.1 c.c. of bottle No. 3; 5 c.mm., 0.5 c.c. of bottle No. 3, etc. It has been customary to designate the dose of tuberculin in grams and milligrams, while the dilutions are almost invariably made by liquid measurement. This makes a difference in the actual amount administered, but the error is small. However, to be consistent I have in this paper adopted the c.mm. as the measure of dosage. The dilutions are best made in wide-mouthed, glass-stoppered bottles. They should be kept in a cool, dark place when not in use. The salt solution must be prepared carefully with distilled water and pure sodium chlorid. Impurities may cause endless annoyance by producing a flocculent precipitate which may not appear until after twelve to twenty-four hours. If the pipets are sterilized there is no danger of contamination. Fresh dilutions should be prepared every two weeks. We have been unable to note change in strength in this period.

To make the dilutions one needs a flask for the sterile salt-carbolic solution, a number of wide-mouthed, preferably glass-stoppered, bottles, and two pipets, one with relative large bore, accommodating 10 c.c of liquid and graduated in tenths of a cubic centimeter, one with finer bore accommodating 0.1 c.c. and graduated in hundredths of a cubic centimeter. The simplest method of procedure is as follows:

To 1 liter of distilled water add 8 gm. of pure sodium chlorid and 2.5 c.c. of pure carbolic acid. Dissolve, filter into a thin flask, and plug the mouth with absorbent cotton. The solution is best sterilized in an autoclave, but boiling for fifteen minutes on two consecutive days suffices. If sterilized by boiling 1,100 c.c. of water should be used to allow for evaporation. It is an advantage to distribute the liter of solution in ten small flasks, each containing 100 c.c., rather than to sterilize it in a large flask. Whenever the tuberculin dilutions are to be prepared a small flask of diluent is used and the remaining portion discarded so that the same flask is never used a second time, and danger of contamination is avoided. Seven bottles are sterilized by boiling, and numbered from 2 to 8, and the date noted upon the label. Into each bottle 9 c.c. of diluent is measured. To bottle 2, 1 c.c. of tuberculin is added and carefully shaken; to bottle 3, 1 c.c. of bottle 2, etc. If only the high dilutions are required it is economical to begin at bottle 3 by using 9.9 c.c. diluent and 0.1 c.c. of tuberculin, and to prepare the higher dilutions as above by adding to 9 c.c. diluent 1 c.c. of the contents of the next lower dilution.

The injections are made subcutaneously, so that when a local reaction occurs it can be readily detected. I have found the Record Syringe the most satisfactory of the many I have used. The injection may be made into any portion of the body, but the region of the back below the angle of the scapula is the desirable situation. Often the arm will be found more convenient, and one need not hesitate to make the injections there. Local reactions follow injections into the arm more readily than injections into the back, and if the reaction be extensive it is far more painful and incommoding upon the arm. The syringe and needle should, of course, be boiled before use, and care should be taken that the tuberculin dilutions remain sterile. The skin needs no other preparation than to be rubbed with alcohol.

Other routes of administration have been proposed. None of these have advantage over the subcutaneous, some are questionably effective, and all have decided disadvantages.

Initial Dose of Tuberculin.—There are two methods used in determining the initial dose:

1. To attempt to estimate the patient's tolerance for tuberculin and inject a dose just short of the one that will cause a reaction.
2. To select a dose that experience has taught to be safely below the reacting dose and rapidly to advance until symptoms of approaching intolerance supervene.

The best method to estimate the patient's tolerance for tuberculin is to perform the intracutaneous test with varying strength of tuberculin. It is convenient to begin with a dilution of 1: 100,000. Since approximately 0.1 c.c. of the dilution is injected into the skin the patient receives 0.001 c.mm. of tuberculin. If the patient reacts to this dose then treatment should be begun with 0.0001 c.mm. tuberculin. Should he fail to react to the 1: 100,000 dilution, then a second test is performed with a 1: 10,000 dilution, and if still no reaction occurs, then another with a 1: 1,000 dilution. If a reaction occurs to the 1: 10,000 dilution, treatment may safely be begun with 0.001 c.mm. tuberculin; if only to the 1: 1,000 dilution, then 0.01 c.mm. may be used as the initial dose. The method is altogether satisfactory and is an accurate way to estimate the proper amount of tuberculin with which to begin treatment.

The test is performed by injecting from a sterile syringe about 0.1 c.c. of a dilute solution of tuberculin through a fine needle, the point of which has been inserted *into* the skin. After cleaning the skin of the forearm with alcohol, it is drawn taut with the left hand held under the arm, and the needle introduced, with the aperture directed toward the outer surface of the skin. If the point of the needle is in the skin a white elevation occurs immediately upon the introduction of the solution, if in the subcutaneous tissue no infiltration is apparent. The test is very delicate, and satisfactory results can be obtained only by exercising extreme precaution. In cleaning the syringes the wash water must not be ejected into the sterilizer. We have been able to obtain satisfactory results only by boiling the syringe used for making the control injection of sterile salt solution in a separate dish in which syringes used for tuberculin injections never come.

The reaction consists of infiltration and hyperemia about the site of injection analogous to the reaction to the cutaneous test. It appears in from six to eight hours, reaches its maximum in from twenty-four to forty-eight hours, and usually disappears in from six to ten days. The injection of sterile salt solution into the skin is followed by a definite traumatic reaction, indistinguishable from a mild tuberculin reaction. This reaction is at its maximum after twenty-four hours, and completely disappears in forty-eight hours. In order to use the salt solution as a control the tests must be read forty-eight hours after they are given.

The second method is entirely empirical. Experience with the various tuberculins has taught us the safe dose for each, that is, the dose that will produce no reaction. Having thus begun treatment at this point the dose is rapidly raised until reactions threaten. In the highly sensitive this point is reached early, in the weakly sensitive not until weeks or even months have passed.

Observers do not agree upon the exact size of the dose best suited to inaugurate treatment, but there is general uniformity of opinion. My experience has been mainly with B. F. and O. T. For B. F. I consider 0.0001 c.mm. the dose generally suitable for beginning treatment. For O. T. 0.001 c.mm. For T. R. and B. E. the initial dose is usually between 0.001 and 0.005 c.mm. It will be remembered that T. R. contains 10 mg. and B. E. 5 mg. of ground dried tubercle bacilli in each cubic centimeter. Some authors have considered it best to express the dose of these two preparations in terms of the tubercle bacillus content, but this method is very confusing. We have adopted the plan of expressing the dose of all tuberculins in terms of dilutions of the marketed product.

It will be seen that the initial dose of all tuberculins is somewhere in the neighborhood of 0.001 c.mm., and it is a satisfactory plan to adopt this amount as the initial dose of any tuberculin. Severe reactions never occur after this dose, and the mild reactions that sometimes follow can do no harm. Brown gives the smallest dose that in his experience caused a reaction as 0.0001 c.mm. B. F. I have seen a local and a slight general reaction in a child to 0.000,001 c.mm. B. F.

Subsequent Doses and Intervals.—The physician has administered the first dose of tuberculin. When shall the second be given, and upon what plan shall the dose be increased? The question of dose intervals has aroused a great deal of discussion. Many advance arguments based upon experimental data to enforce their contention, but in the end we have accepted the verdict of empiricism and adopted the interval that practice has found most satisfactory.

Those who follow Wright select ten days as the best general interval. They conceive each tuberculin injection to be followed by a short negative phase, then a rapidly rising positive phase, and a slow return to the previous level. The full play of this immunity response, they think, requires ten days, and they do not inject a second dose until the effects of the first have worn off.

Pickert advises an interval of from sixteen to twenty-eight days between doses, claiming that he finds the formation of antituberculin to reach its high point during that period. I have already spoken of the method used to demonstrate antituberculin, and have said that the results are inconclusive.

The empirical results of clinicians have made the selection of from three to five-day intervals almost universal. Some observers hold to these doses throughout, others lengthen the interval when larger doses are reached. To be consistent a regular interval should be adopted, but in institutional work, and even in private practice, it is a great convenience to select two days of the week for tuberculin administration. That one dose is given at a three-day interval and the alternate dose at a four-day interval has, as far as we can judge, no effect upon the result of the treatment.

Our routine method is to administer the small doses twice a week until we have reached the level of the patient's tolerance, when we change to the week interval. If the patient shows no evidence of intolerance we change to the week interval when 10 c.mm. is reached.

In the section on the principles of tuberculin treatment I pointed out that our aim should be to get the greatest amount of focal stimulation without liberating general reactions. To apply this principle each patient should be studied individually, and the signs that indicate an impending reaction carefully watched for. I am convinced that with care this balance may be satisfactorily maintained. Therefore, before speaking of an outline for raising the dose I must point out in detail the symptoms by which one may know that the limit of tolerance has been reached.

Tuberculin Reaction.—The symptoms of a tuberculin reaction may be divided conveniently into three groups: (1) the general constitutional symptoms; (2) the focal reaction or changes that occur about the diseased area; (3) the local reaction or changes that occur at the point of injection.

The constitutional symptoms are manifold and varied. They consist usually of a rise of temperature and pulse rate associated with one or more of the following symptoms: chilliness, general malaise, headache, general aching, pain in the joints, loss of appetite, nausea, and vomiting. After a severe reaction there is usually a loss of weight.

The focal reaction consists of inflammatory changes about the lesion. When the lesion is situated externally the reaction is easily appreciated, but when the focus is in an internal organ even severe reactions may go undetected. Koch's description of the reaction in lupus gives a good picture of the changes.

> "A few hours after the injection the diseased skin becomes red and swollen. As the temperature rises the swelling and redness increase and may reach such a marked degree that the tissue becomes brownish-red and necrotic. With the fall of temperature the swelling decreases and in a few days may completely disappear. The lupus areas are covered with crusts which dry and fall off, leaving, sometimes after a single injection, a smooth pink scar. It is remarkable how absolutely specific is the selection of tuberculin for tuberculous tissue; none of the surrounding skin or old scars shows the least evidence of reaction."

The symptoms associated with such a reaction depend upon the site of the lesion. For instance, in pulmonary tuberculosis they are pain, increase of cough and expectoration, and changes in the previously observed physical signs; in tuberculosis of bone and joint, increased redness, swelling, heat and pain, with more evident limitation of movement and the appearance or increase of crepitus; in tuberculosis of the genito-urinary organs, pain, swelling, increased secretion, bleeding, increased frequency and pain on urination.

The local reaction consists of pain, soreness, redness, and swelling at the point where the tuberculin is injected.

In tuberculin treatment we wish to avoid tuberculin reactions, and therefore do not push the dose until these frank manifestations of a reaction occur. Nevertheless we look to these various manifestations in mild forms as the signal of approaching danger.

Of the constitutional symptoms the most helpful guide is the temperature. It is the only phenomenon that we can accurately measure, and is the one that most commonly occurs as an isolated signal. For this reason we give it careful attention. Patients taking tuberculin should, with few exceptions, keep a daily record of their temperature. To facilitate such record-keeping special forms have been devised. We have found a record book modeled after one used by Brown to be satisfactory. The accompanying sheet (page 613) is a specimen page. On the inside of the cover the following directions are printed:

INSTRUCTIONS

"Now that you are to begin to take tuberculin it is important that you pay the greatest attention to keeping this record carefully and conscientiously. Whether we increase or decrease the amount of tuberculin you are receiving will depend entirely upon how you have stood the preceding dose, and the only way we can judge of this is from the record you keep. Your improvement depends, then, to a large extent upon the faithfulness with which you keep your record. Never put down a temperature unless you are sure of it, and never make any entry until you are sure that you understand the book.

"Each page in this book will keep your record for a week.

"As you see, there are seven columns. Put the date at the top of the column, and make a note after each symptom in the space immediately opposite it. You fill in each space every day, except the 'tuberculin' space, which the doctor will fill in. After each symptom, if you have it, make a + mark. If you haven't it make an O. After 'appetite,' 'digestion,' 'sleep,' write 'good' or 'poor,' as may suit the case. Under the heading 'rest' write how many hours spent in bed, how many in resting in a chair. In filling in the number of hours spent in the open air include those spent in bed if you sleep on a porch or with your windows out. Under 'diet' put down the number of pints of milk, the number of eggs and the number of tablespoonfuls of oil. If you have any symptom, no matter how trivial it may seem to you, which is not in this book, tell the doctor about it at your next visit."

Elevations even of a few fifths of a degree above the usual maximum temperature should receive careful consideration and their relation to the injection should be studied. As isolated phenomena they do not necessarily indicate a tuberculin reaction, but their presence should arouse our suspicion, and if other symptoms accompany the rise we must proceed more cautiously with the treatment. If the temperature has been constantly subnormal with wide daily variations in range, under treatment the mean level may rise gradually toward normal and the oscillations become smaller. Such an occurrence must be viewed as a favorable effect of the treatment.

As is well known, patients with tuberculous lesions, and particularly patients with pulmonary tuberculosis, seldom have a constantly uniform range of temperature. Besides the usual variations in the daily oscillations their temperature balance is easily disturbed by a variety of conditions. There is no feature of tuberculin treatment more difficult than to estimate justly the relation of such disturbances to tuberculin administration. Certain general features aid us. Most helpful of these is careful observation of the point of injection. As our experience grows we emphasize this association more and more. Febrile reactions to tuberculin seldom occur without an accompanying local reaction unless preceding injections have been followed by local reactions. Not uncommonly a number of injections are followed by soreness and swelling, then suddenly when the dose is raised or repeated a general reaction supervenes, although after this particular injection no local changes occur. Denys refuses to consider any febrile elevation coming on after forty-eight hours, due to the tuberculin injection. However, Brown believes it may be delayed for from forty-eight to sixty hours. I have never observed a reaction to tuberculin come later than thirty-six hours after the injection.

Temperature elevations occurring during tuberculin treatment, and not due to the injections, may be grouped in three classes: (1) Temperature elevations due to external influences, overexertion, fright, emotions. An unexpected visit may produce a decided rise, as may an animated conversation or excitement, as over a game of cards. (2) Sometimes it is not possible to ascribe the temperature elevation to any definite cause. Such temporary elevations are now interpreted as evidence of auto-inoculation. On account of changes, probably circulatory, about the lesion, absorption is suddenly increased and the patient has an endogenous tuberculin reaction. Indeed such reactions often present the characteristic earmarks of a tuberculin reaction, and, aside from the absence of the local changes, are indistinguishable from it. To this mechanism is ascribed the fever following exertion. This conception is the foundation of Patter-

DATE:								
TEMPERATURE	8 A. M.							
	12 M.							
	4 P. M.							
	8 P. M.							
PULSE:	8 A. M.							
	12 M.							
	4 P. M.							
	8 P. M.							
WEIGHT:								
TUBERCULIN:	Dose							
PLACE OF INJECTION:	Pain							
	Swelling							
	Enlarged Glands							
SYMPTOMS:	Appetite							
	Digestion							
	Nausea							
	Vomiting							
	Headache							
	Chilliness							
	Pain in Joints							
	Sleep							
	Nervousness							
STRENGTH:	As usual							
	Increased							
	Decreased							
COUGH:	As usual							
	Increased							
	Decreased							
SPUTUM:	As usual							
	Increased							
	Decreased							
	Blood in Sputum							
	Pain in Chest							
	Shortness of Breath							
REST:	In Bed							
	Sitting Down							
	Exercise							
	In Open Air							
DIET:	Milk							
	Eggs							
	Oil							
	Total Gain in Weight							

son's method of treating tuberculosis by graded exercise. (3) Intercurrent infections are a fertile source of temperature elevation. The beginning of an attack of tonsillitis, of grip, or of any infection may cause alarm until the course of events decides the diagnosis.

During a tuberculin reaction the pulse usually follows the temperature curve. Bandelier and Roepke regard an increase in the pulse rate as a solitary signal of great importance. I cannot confirm this observation, though I admit I have paid less heed to the pulse than to the temperature.

The other constitutional symptoms need not be regarded separately; they may be considered as a group under the head of intoxication. I use the term intoxication in a descriptive, not a literal, sense. After tuberculin administered subcutaneously for diagnosis, patients often complain of general indisposition and malaise, though there is no rise of temperature. Occasionally during tuberculin treatment similar symptoms occur. The condition is ill defined and cannot be described with precision, but the patient complains of not feeling so well as usual, of depression, of loss of appetite, of headache, and of nervousness—symptoms indefinite enough, it is true, but worthy of consideration, and, when combined with loss of weight, of great importance. Indeed, loss of weight as an isolated symptom is sometimes the first warning of intolerance. It is, however, more valuable as a sign of overdosage late in treatment than as a protection against suddenly appearing reactions. I have found that tuberculin intolerance to small doses manifested by symptoms of intoxication and without an accompanying local reaction occurs commonly at the beginning of treatment. Patients displaying such reaction often have a little fever and other symptoms of intoxication before tuberculin is begun, and the injections simply aggravate these symptoms. Apparently these patients have too little resistance to respond to tuberculin injections with a frank local reaction.

The focal reaction is of some value in guiding dosage when the lesion is situated externally. In my experience local or slight general reactions nearly always precede visible focal reactions, but in localized tuberculous lesions we have less fear of deleterious effects from general reactions than in pulmonary tuberculosis, and we may push on through local reactions until focal changes occur or a severe general reaction arrests our efforts. This is not good practice for routine cases, and should be used, if at all, under special conditions. As regards pulmonary tuberculosis I have never observed changes in the physical signs that could be interpreted as indubitable evidence of a focal reaction in the absence of constitutional symptoms. I say indubitable evidence because the question of the interpretation of pulmonary focal reactions is variously answered. For instance, Otten is satisfied to draw such an important conclusion from slight changes in the percussion note. I have not attained such astonishing finesse. Nor am I willing to follow Roepke, who accepts changes in the character of the breath sounds as sufficient evidence. I regard the appearance of fresh râles as the only reliable mark of a pulmonary focal reaction.

Lastly, we come to a consideration of the local reaction which is the most valuable of the three in calling our attention to the proximity of the border-line of tolerance. In speaking of elevations of temperature I emphasized the importance of the local reaction as an aid in their interpretation, and said that general reactions practically never occur without local changes to preceding doses. Since we have paid special attention to the local reaction as a guide in treatment I have never missed this relation.

Local changes must be looked for carefully, and the site of the previous injection always inspected before the following dose is administered. Usually patients complain of a little tenderness when the reaction is slight, of severe pain and of swelling when intense. However, though they make no complaint, inspection may reveal more or less swelling and induration. When such local changes are observed we must proceed cautiously if we wish to avoid general reactions. If the dose be raised or the size of the local reaction increase with succeeding injections of the same dose, general reactions are imminent.

I must point out that all regions of the body are not equally sensitive to tuberculin. This interesting fact has been studied with the cutaneous reaction, and applies equally to subcutaneous injections. Local reactions occur much earlier when injections are made in the arm than when the back is selected. For this reason we prefer to administer tuberculin in the subcutaneous tissue of the back. From the importance attached to the local reaction as a guide to tuberculin treatment it is evident why I have emphasized that injections should be made subcutaneously.

With a clear appreciation of the signals of approaching danger the physician is in a position to push on with tuberculin treatment. The initial dose has been administered and a bi-weekly interval decided upon. His first duty is to avoid reactions, but it is scarcely less important to carry the patient as quickly as possible to the point of his tolerance, the point where tuberculin gives its best results. Thus the aim of treatment is clear, though its application is individual. The benefits of tuberculin treatment cannot be measured in terms of the quantity of tuberculin administered, for a large dose to one patient has the effect of a smaller one to another. Each appropriate dose has its own full value, and the benefits of treatment are derived throughout the course and are not summed up in the size of the final dose. Many patients who never get beyond a moderate dose are as happily influenced as others going uninterrupted to large amounts.

The fundamental secrets of tuberculin treatment are now revealed, and perhaps it is superfluous to develop them further. However, experience has suggested a number of interesting details in the application of the principles, and it will be helpful to review them.

During the preliminary period of small dosage it is safe and, I think, advisable to double the amount of each injection until symptoms warn that the level of tolerance has been reached, or if these do not appear until 0.1 c.mm. is reached. It is indeed very arbitrary to select 0.1 c.mm. as the dose beyond which we must proceed with greater caution, but experience has taught us that reactions occur more commonly to doses from 0.1 to 10 c.mm. than at any other level. It is the period that requires the greatest vigilance, for when 10 c.mm. is passed progress from then on is usually unobstructed. When 0.1 c.mm. is reached the dose may be increased by tenths. This plan, however, has evident disadvantages, since the increase from 0.1 to 0.2 c.mm. is a 100 per cent increase, while from 0.9 to 1 c.mm. is but 1/11 per cent increase. In support of this objection I may say that when the plan is followed reactions are particularly apt to occur after the first large increase. To obviate this inequality the first and second jumps may be divided and the latter lengthened. Thus we would give 0.1, 0.15, 0.25, 0.3, 0.4, 0.5, 0.7, 1.0, etc. This plan is simple, and in practice works well. To make the increase of dosage equal Brown has devised logarithmic scales. He writes:

> "It is intended merely as a suggestion in controlling the dosage, which for each patient varies greatly, according to individual susceptibility, and is of use in giving any tuberculin, for all tuberculins are either in solution or suspensions in fluids. This scheme computed by Pope is based on a logarithmic scale, and is so arranged that in going from 0.1 to 1 c.c. of any solution two to twelve doses may be employed, while the rate of increase of dose is always constant. The average patient, in the writer's experience, can take the sixth scale (six doses to each solution) without any danger of reaction, but some must go more slowly and a few, especially during a second course, may go more rapidly."

Doses (Logarithmic Scale)

2	3	4	5	6	7	8	9	10	11	12
1	1	1	1	1	1	1	1	1	1	1
3.2	2.2	1.8	1.6	1.5	1.4	1.3	1.3	1.3	1.2	1.2
10	4.7	3.2	2.5	2.2	2.0	1.8	1.7	1.6	1.5	1.5
	10	5.6	4.0	3.2	2.7	2.4	2.2	2.0	1.8	1.8
		10	6.3	4.7	3.7	3.2	2.8	2.5	2.3	2.2
			10	6.8	5.2	4.2	3.6	3.2	2.9	2.6
				10	7.2	5.6	4.7	4.0	3.5	3.2
					10	7.5	6.0	5.0	4.3	3.8
						10	7.7	6.3	5.3	4.7
							10	8.0	6.6	5.6
								10	8.0	6.8
									10	8.3
										10

If at any time during the course of treatment symptoms of reaction appear progress thereafter must be very cautious. As I have stated, local changes are usually the first evidence of approaching intolerance. At times the local reaction increases with each succeeding injection, even though the dose be not raised; again, it may decrease with later injections and the period of threatening intolerance be quickly passed. If the dose has been rapidly raised a constitutional reaction may occur with the first local reaction. Following this plan, it is often possible to raise the dose uninterruptedly until large amounts are reached.

When symptoms of tuberculin reaction appear in the absence of a general reaction the further course will depend entirely upon the behavior of the patient. The behavior of patients at this point may be roughly grouped into four types, if you will remember that the dividing line between the groups is very elastic.

1. In a number, by slowly and cautiously raising the dose, this early period of hypersensitiveness is soon overcome, and thereafter we can rapidly rise to higher doses.
2. In a number of cases the patient's sensitiveness remains at a remarkably constant level, so that any effort to go beyond a certain dose is invariably followed by a general reaction. Such instances are not isolated, and a constant level hypersensitiveness may persist for years.
3. There are patients who persistently remain at a given level, but under prolonged treatment gradually acquire a lower hypersensitiveness, and the doses may then be gradually increased. In our experience such a change in hypersensitiveness is usually associated with a marked improvement in the patient's condition.
4. In a relatively small number of patients the measure of their tolerance is reached early, and either it is impossible to advance the dose without producing disagreeable symptoms or indeed in some further treatment increases the hypersensitiveness, and it is necessary to retreat to smaller doses or abandon tuberculin altogether. In our experience such patients rarely do well under any treatment.

The fourth group has received extended consideration under the caption of the supersensitive state. In this condition all efforts to push treatment are without avail; indeed, our efforts but increase the intolerance. For instance, a patient may be started with a dose of 0.001 c.mm. and take increasing doses without apparent effect until 0.02 is reached, when a marked local or mild general reaction occurs. Upon repetition of the dose a more marked reaction occurs. The dose is decreased to 0.01 c.mm., and reaction follows again. At the next injection 0.005 c.mm. is given; again a reaction follows. Though the patient at first took 0.001 c.mm.

without effect, now 0.0001 c.mm. may be followed by local swelling and soreness. This condition of increased sensitiveness is nearly always accompanied by symptoms of intoxication. As I have said, Löwenstein advises a rapid increase of dosage because he believes small doses, and particularly small doses long continued, favor the development of supersensitiveness. My experience does not confirm this view, for it indicates that supersensitiveness is commonly the result of overdosage and occurs particularly after severe general reactions.

In pulmonary tuberculosis when increased activity of the disease supervenes, an increase in tuberculin hypersensitiveness nearly always accompanies it.

When tuberculin treatment is carried on in the cautious manner previously outlined, general reactions seldom occur, and severe general reactions are very exceptional. However, even with the greatest caution it is impossible to avoid general reactions completely. As long as they are mild no harm will be done. When general reactions occur tuberculin should be omitted for at least two weeks and then treatment be begun at a much smaller dose. Particular watchfulness is needed when approaching the dose that occasioned the reaction.

Should an intercurrent infection occur during treatment it is advisable to discontinue tuberculin temporarily until convalescence is established and then begin at a much smaller dose and again gradually increase the amount. During intercurrent infections tuberculin hypersensitiveness is variously influenced. During measles, as von Pirquet has shown, hypersensitiveness is obliterated, to appear again during convalescence. Hamberger has noted a similar diminution of sensitiveness in pneumonia, diphtheria, scarlet fever, and cerebrospinal meningitis. However, during convalescence hypersensitiveness is often reëstablished at a higher level than before the illness. Many authors have directed attention to the unusual frequency of conjunctival tuberculin reactions during convalescence from typhoid fever.

Terminal Dose.—The physician is now in full swing with tuberculin treatment. How long shall the treatment be continued and at what dose shall he halt?

From what has been said it must be evident that neither question can be answered directly. Tuberculin benefits accrue slowly and, since the infection is chronic and at best heals but slowly, abrupt improvement cannot be expected. Nor, again, will a few doses of tuberculin accomplish appreciable results. Nor, yet again, as I have frequently emphasized, does any particular dose of tuberculin measure the benefit that has been obtained. I never advise tuberculin unless there is reasonable assurance that treatment will be persistently followed for at least six months. If conditions are favorable I like to give tuberculin continuously for from nine to twelve months. At the end of that period I prefer to stop treatment and to take it up again if it seems advisable after an interval of from three to six months. I can give no satisfactory reason for this preference other than clinical impressions, and I admit the ground for these is not very solid.

Petruschky is a stanch advocate of intermittent treatment. He calls his plan the "etappen-kure." Treatment is administered for three months, then an interval of three months is interposed, again three months of treatment, and so on.

There is no absolute terminal dose, although custom has set certain precedents. Most observers cease raising the dose when 1,000 c.mm. is reached. Often this dose is exceeded. Denys has given as much as 10 c.c. B. F. However, the sum of clinical experience is that the average patient seems to lose ground when a dose of 1,000 c.mm. is exceeded. When this maximum is reached some clinicians advise repeating it indefinitely at ten to fourteen-day intervals; others advise breaking off treatment at least temporarily.

Jochmann has sought to put the question of the terminal dose upon a more satisfactory basis. He proposes stopping the treatment at the point where the cutaneous tuberculin reaction is lost. He finds this point to be between 300 and 500 c.mm. O. T.

A course of tuberculin treatment extending over a period of from six to twelve months does not cure tuberculosis. Often the symptoms completely disappear, though the lesion persists. In other instances the lesion may be apparently healed, but we fear a fresh outbreak. Does a single course of treatment give all the advantages that tuberculin may confer? Again we must confess that we can give no more satisfactory answer to this question than to others that have been asked. However, most clinicians are in favor of repeated courses of treatment. I stand committed to this sentiment and feel that I have seen benefit follow the administration of tuberculin interruptedly over a number of years. Petruschky, Bandelier and Roepke, and Brown believe in applying the subcutaneous test some time after treatment has been stopped, and if the patient reacts advise another course.

If it is decided to give a second course of tuberculin, treatment may be pushed more vigorously. We find that as a general rule the tuberculin tolerance developed under tuberculin treatment persists for a very long time, often unabated for a year. Also we have gaged the patient's tolerance for tuberculin. Therefore, treatment may be begun at a higher dose and the doses more rapidly raised.

DRUG TREATMENT

For centuries therapists have been seeking a specific remedy for tuberculosis. The number of drugs which have been tried and found wanting is legion. When the causative agent of tuberculosis was discovered by Koch in the tubercle bacillus a definite point of attack was established, and the object of drug therapists at once became that of finding some antiseptic agent capable of killing in the tissues the invading organisms. For this purpose numerous agents, known to kill the tubercle bacillus experimentally in vitro, have been administered by mouth, by inhalation, by subcutaneous, intravenous, or intratracheal injection, or even by direct injection through the chest wall into the pulmonary tissue. None of these attempts has been successful enough to stand the test of time. The idea is perfectly logical and is analogous to the quinin treatment of malaria or the mercury or arsenic treatment of syphilis. Unfortunately, however, there are insurmountable difficulties in the way of applying any specific drug treatment to pulmonary tuberculosis. The tubercle bacillus is much more resistant, probably on account of its capsule, to all disinfecting agents than are most other bacteria, and it seems unlikely that any agent will be found which can be used in sufficient concentration to kill the tubercle bacillus without seriously injuring the host. Furthermore, the pathology of tuberculosis is such that the bacilli have their residence either in dead or dying caseous material or within the fibrous, non-vascular tubercle, alike inaccessible either by the blood stream or by the inspired air. Although prediction is always hazardous, yet it seems extremely improbable that the future holds any promise for this method of attack upon tuberculosis, or that any specific drug therapy will ever be one whit more successful than have past efforts. Not a year passes, and undoubtedly not one will pass until the scourge of tuberculosis has at last been conquered, that new "tuberculosis cures" are not put forward, enthusiastically advocated, and widely exploited, only to fall by the wayside after a longer or shorter vogue, and have their places taken by others of no greater worth or permanency. Among such "false specifics," as they have been aptly termed, may be mentioned creosote, alcohol, cod-liver oil, arsenic, cinnamic acid, iodin, ichthyol, calcium, silver, carbolic acid, camphor, formaldehyd, turpentine, phosphorus, mercury, lecithin, radio-active compounds, etc.

The wise physician will exercise a well-founded skepticism and, in view of past failures in this field, will refuse to be carried away by glowing accounts of marvelous curative properties in this or that new drug.

This criticism of drug therapy is aimed solely at the drugs used as specifics, those for which the claim is made that they exert any directly curative effect on tuberculosis. In the symptomatic treatment a few drugs are of considerable value. These will be considered under that heading. Undoubtedly many patients have been harmed by overdrugging, and in general it is a good maxim to avoid the use of drugs when other measures will suffice.

TREATMENT OF PULMONARY TUBERCULOSIS

Application of Fundamental Principles of Treatment

I have discussed the fundamental principles of tuberculosis treatment and I shall now illustrate their application to the most prevalent form of the infection and the one that concerns particularly the internist and general practitioner. Even though these principles be applied somewhat in detail, still it will be possible only to treat some of the more conspicuous among the innumerable problems the practitioner must meet. Indeed every case presents a problem which in the combination of details differs from the problem presented by any other case. The practitioner must have clearly in mind the abstractly desirable thing to do. This must ever be the guide to action even though it be necessary, as it usually is, to modify this abstract plan by various and sometimes divergent expedients. However, with an abstract plan tenaciously held, these expedients will be suspiciously entertained and grudgingly granted. The practitioner is constantly attacked by solicitous influences which though interested and well meant nevertheless tend to undermine his morale. Often a too-ready pliancy, an unconscious drift towards complacency, a natural desire to please and sometimes sheer exhaustion before the interminable battery of pleading, suggestion and demand from patient, family and friends lead the physician to yield against his better judgment. A firm grasp of the principles of treatment and a conviction of their efficacy is the surest support against such weakness. Still the physician must not be too rigid and implacable.

In the treatment of tuberculosis perhaps more than in the treatment of any other disease he must consider the peculiar circumstances of the individual patient and be willing to hear and carefully weigh every objection to the measures he proposes. Some of these objections may be brushed aside as trivial or irrelevant; others may be important enough to warrant modifying details; some may be sufficiently grave to require a radical change in the whole plan. It is impossible to lay down rules to meet all of these contingencies satisfactorily. Only a few can be touched upon, the rest must be left to the experience, skill and good sense of the practitioner.

Let us assume that a diagnosis of pulmonary tuberculosis has been accurately made and the physician stands confronted by the problem—What is now to be done? Let us assume further that the patient has outspoken pulmonary tuberculosis and reserve to be discussed later that important group in which tuberculosis is suspected or even confidently thought to be present but cannot be unquestionably demonstrated. There are certain simple yet important measures to be taken in all cases irrespective of the extent of the disease, the character of the symptoms or the social station of the patient.

As soon as a diagnosis of pulmonary tuberculosis is made, the patient should be put to bed. It usually requires a week or longer to come to a final decision about the plan of treatment to be adopted. During this period much harm may be done if the patient is allowed to go about unprotected. It is a period of much physical and nervous strain. There are many important advantages to having the patient quiet in bed. It begins at once the proper treatment for the disease. The patient is at rest and the harmful effects of fatigue are removed. Nervous strain can also be reduced to a minimum by careful management of the situation. Unending explanations about the condition and the assurances and reassurances of friends are avoided. Most of the further arrangements for treatment can be made without troubling the patient unnecessarily with details. It provides an opportunity for the physician to make important additional observations, the course of the temperature and pulse rate and the progress of other symptoms. After the arrangements for treatment are completed, the patient may then, if his condition warrants it, make such business and household adjustments as the circumstances demand, leaving his bed if necessary only to return at once when the affairs that call him away are completed.

When the patient is put to bed he and responsible members of the family should be informed about the nature of the disease and the general plan of treatment to be followed. In adults only rare circumstances may justify departing from this rule. It has the sanction of all well-qualified physicians and even slight experience in the management of tuberculous patients will demonstrate how necessary it is for holding the confidence of the patient and encouraging his intelligent coöperation. Its value is so self-evident that I should not comment upon it were it not for the fact that physicians are still frequently besought to hide the real nature of the symptoms from the patient. In patients affected by an acute rapidly fatal form of tuberculosis such charitable deception may be justified. However, an unwillingness to tell the patient frankly about the nature of his disease is equivalent to a confession of utter hopelessness on the part of the physician. For as long as there is any hope that treatment may avail, the patient must understand the object of treatment and actively coöperate in its execution. It is hardly necessary to add that tact and kindly sympathy should temper the professional revelations. Different patients must be dealt with differently. This is one of the details of personal relation between physician and patient which experience mellows but no instruction can teach.

The patient is now under treatment and knows in a general way what he must face. Much of the further detail of treatment may be thrashed out with responsible members of the family and a settled plan be submitted to the patient for approval. The first question to be decided is whether the patient shall be treated at home or sent off to an institution or resort. Leaving aside for the moment all qualifying circumstances I am convinced that as a general proposition it is a decided advantage for patients to be treated away from home. One factor in forcing this opinion upon me is my observation that most practitioners treat tuberculosis very badly, while in contrast it is treated very well at most sanatoriums and tuberculosis resorts. But even if we disregard a comparison of professional qualifications and assume them to be equal under both circumstances, still I believe treatment away from home has advantages. Most homes are poorly adapted to care for the sick. The service though willing and lovingly bestowed is inexperienced and undisciplined. Again, it is difficult for the patient to secure *rest* in the home. This is a matter of common experience. Every sight, every sound recalls the details of accustomed routine. The quarrels of the children, the complaints of servants, telephone calls, friendly visits, messages from the office, the postman's knock, all constantly remind of the life going on about from which he is debarred. Add to this homely, but in health not unpleasant, whirr of the household wheels in their daily labor, the jar of unavoidable household tragedy, the anxiously awaited servant who does not come, the sick child, the overworked, harassed wife, and the situation is not alluring. The patient is in bed but he is not resting, instead he is fretted and irritated. If he has reached the stage where he feels well he is hardly human if at the onset of a tragedy he does not rise from his bed and take his place beside the family to help repair the disaster. If this be in a measure true of the father of a family, what shall we say of a mother! A household must be exceptionally organized in which a mother can go to bed and rest for a long time. Similar objections, though not to so pressing a degree, may be suggested even for the less responsible members of the household. Most people experience a very great sense of relief when the habitual responsibilities and cares of life are left behind and they can then settle down to a long and tedious treatment with more calm resignation.

In addition to these great advantages of sanatorium or tuberculosis resort treatment, there are still others. The patient is surrounded by those subjected to the same discipline and a routine which at home runs counter to the habits of life about him and is conspicuous and unnatural on account of this distinction is there the accepted mode. This makes it much easier to carry out the treatment consistently and faithfully because others about live in the same manner. Lastly I wish to emphasize the very great educational value of a residence at a sanatorium or tuberculosis resort. The seriousness of the disease and the value and importance of treatment are lessons so thoroughly learned that they are inerasable from memory. I find that it is very easy to advise and control patients who have had this training. They see at once the reasonableness of the advice and are faithful in carrying it out.

Although I firmly believe that the sanatorium or tuberculosis resort offers distinct advantages over the home in treating tuberculosis, it must not be inferred that every patient with the disease must be rushed off as soon as the diagnosis is made. Nothing could be more imprudent or disastrous than such a practice. Patients with small lesions and only slight symptoms may be sent off promptly after the necessary preparations have been finished. The necessary preparations include detailed arrangements for the itinerary and for the proper reception of the patient at his destination. A physician has not only failed in his duty to the patient but is guilty of gross neglect if he tells a patient to go here, there or elsewhere without being informed about the conditions that exist at the chosen location or without having made in advance arrangements for his immediate accommodation and medical care. It is often disastrous for a patient to arrive at an unknown and distant place, ignorant of living conditions, of the expense that must be incurred, of the physician he should consult. Sometimes he innocently falls into the worst possible surroundings and under indifferent medical care and all the profit that might have come from the journey is quickly and irrevocably lost. No man would send off a dollar bill with the complete unconcern with which thousands of tuberculous patients are sent off to seek recovery. It is thoughtlessly assumed that in some miraculous way they will be guided to a delightful haven of rest and comfort where they will repose safely in the care of an angel of a doctor. In many instances the necessities of life are unprovided for, as though the patients were to be fed as Elijah was fed in the desert. As a matter of experience they are not guided in this safe way nor are they so fed. Sometimes patients who at home are so ill they can hardly drag about are sent off with funds only sufficient to support them for a few weeks. The guilty physician must think that a few lungfuls of salubrious air will invigorate the patient's tottering frame and weary mind and fit him in a trice to take his place in the active competition of life. And yet it is well known that no such magic air exists. Or else he must think that tuberculosis resorts are large charitable establishments where board, lodging, nursing and medical care are gladly and freely bestowed. And yet again it is well known that no such eleemosynary communities can be found. Before a physician starts a patient from home he must see to it: (1) that the journey has been properly planned to insure the comfort of the patient; (2) that suitable accommodations await the patient upon his arrival; (3) that a competent physician is aware of the patient's plans and will be ready to assume immediate medical care of the situation; (4) that some responsible person understands the financial obligations the patient is assuming. If the physician is unfamiliar with conditions at the place to which the patient is going, he must inform himself about them or else refuse to assume responsibility. If he does not personally know the physician to whose care the patient is being intrusted, it is his duty to investigate his qualifications. If he does not know the cost of living and proper medical care, he must take pains to learn it.

Patients who are acutely ill should not be sent off to a distance until they show unmistakable signs of improving and are sufficiently recovered to make the journey with safety. Only occasionally do circumstances arise that make it advisable to break this rule. Unless such circumstances exist the only other excuse for sending bedridden or acutely ill tuberculous patients about the country would be a belief in the extraordinary efficacy of climate. Such childlike credulity is contradicted by universal experience and can no longer be tolerated. Fortunately the heartbreaking spectacle of advanced consumptives traveling about in the vain hope of finding the curing climate is no longer as common as it was in former years. However, the practice has not been wholly abandoned and it is sometimes incredibly difficult for a physician to oppose the insistent demands of relatives. Since climate per se has only slight, if any, value in the treatment of tuberculosis, the acutely ill tuberculous patient will recover as well at home as away, provided he be treated equally skillfully. If treatment cannot be carried out satisfactorily at home, it should be managed at some near-by hospital or sanatorium. Should treatment prove unavailing and the patient gradually grow worse, the physician should oppose suggestions to send the patient away unless some concrete advantage is gained by the change. Should the patient improve, traveling should be postponed until all important constitutional symptoms have disappeared or at least abated.

Numerous circumstances will influence the physician's choice in selecting the location to which to send the patient. Climate is one of the less important ones. More important are the distance from home, the finances of the patient, the accommodations to be obtained, the professional skill of available physicians. Most states now support well-run sanatoriums where treatment can be obtained at little cost. These institutions greatly simplify the task of the physician. At the better tuberculosis resorts the expense of residence is not less than thirty dollars a week. At most of them more expensive accommodations are available that include every comfort and luxury. The amount of money a patient should spend upon the stay away from home should be carefully considered. Every prudent physician knows that tuberculosis is not cured in six months and a patient must reckon with a reduced earning capacity after his return home. Not infrequently a patient will spend all he has saved or borrowed upon a short but expensive visit to a resort and on his return be obliged to go back at once to full work long before his condition warrants the effort. The patient must understand that treatment cannot stop at the end of a few months and he must husband his resources to meet further obligations. Next to financial considerations the most prominent is the skill of the physicians practicing at a given locality. I have already said enough upon this score to indicate the great importance I put upon this factor in influencing our choice. As I have pointed out it is the chief element in the influence of climate. Every physician must investigate the professional qualifications of men practicing at sanatoriums and resorts and intrust patients only to those in whom he may place entire confidence.

Even with the aid of sanatoriums and health resorts, there is still ample opportunity for the practitioner to exercise his skill in treating tuberculous patients. He must care for them before they go away and again upon their return and continuously for the large number who will be under his care throughout their illness. The first step in caring for a patient is to select proper living quarters and to rearrange the household organization to meet the new demands. In well-appointed homes and in families able to provide a nurse, these rearrangements are easily made. If possible two rooms should be provided, a living room and a sleeping room. If the two adjoin and the bed can be rolled from one to the other it is a great advantage. Two rooms are always desirable, but their value is particularly great during the winter months. If a suitable porch or balcony is available this will make an ideal sleeping and resting place. If only one room can be taken over by the patient it should be a bright room with windows on at least two sides. The bed should be comfortable with a tight spring and good mattress. A single bed with wheels so that it can be easily moved about is desirable. An excellent bed for the purpose is a modified Gatch bed manufactured by The Simmons Bed Company. This permits adjustments that allow the patient to assume any position with comfort. Later when the patient is allowed out of bed a suitable reclining chair must be provided. The Adirondack Recliner is the best I know of. The advantages of two communicating rooms or of a room and porch are obvious. One room is arranged so that it may constantly be kept open to the air; the other is warm and comfortable. The patient is prepared for going out in the warm room and then rolled into the open. For dressing, meals and other purposes he may at a moment's notice be returned from out of doors to the warm room.

It is impossible to lay down specific rules for keeping patients in bed. This must be left to the judgment of the physician. However, it is never possible to rest too much or too long. If an error is to be made let it be on the side of resting more than may be absolutely necessary rather than less. In practice the error is almost always made on the wrong side. A few general suggestions may be helpful.

1. When a diagnosis of pulmonary tuberculosis is made the patient should be put to bed for at least one month even though he may have no

fever and all symptoms of the infection rapidly subside. If there has been much loss of weight the period should be longer.

2. Every patient with fever should be kept in bed until the temperature has not exceeded normal at any time of the day for at least two weeks and the pulse rate has fallen to 80 or lower.

3. After an hemoptysis the patient should be kept in bed for at least three or four weeks after the bleeding has stopped.

4. Rest in bed is the best treatment for many of the troublesome symptoms of pulmonary tuberculosis even though the patient may be afebrile.

These periods of rest represent the minimum requirements; they might without harm be lengthened; and in all circumstances of doubt they should be unhesitatingly prolonged. How complete rest in bed should be must be decided for each patient. If the fever is not high he may sit up in bed for meals, go to the toilet, read and so on. If, however, the constitutional symptoms are more marked this latitude cannot be allowed. If they are severe the patient must be treated with the same extreme care as is, for instance, bestowed upon patients with typhoid fever. Sometimes intractable fever, even though not very high and in patients otherwise not very ill, will yield only when such rigid methods are adopted. While in bed the patient should spend the greater part of the twenty-four hours in the open air or as nearly in the open air as can be imitated in a room. In warm or temperate weather this may be done without the least difficulty, but in cold weather special care is required in dressing the patient and arranging the bed to allow him to be out with comfort. It is impossible to discuss these details here. They may be found in many of the books prepared for the use of patients and I recommend as particularly satisfactory *Rules for Recovery from Tuberculosis* by Lawrason Brown. While the patient is in bed special attention is usually demanded by dietary considerations. In some the appetite and digestion are unaffected and they may eat as do healthy persons. But many with fever and most who are seriously ill complain of loss of appetite and various digestive disturbances and the problem how best to overcome these obstacles is indeed difficult and puzzling. Perhaps enough has already been said upon this topic in a previous chapter. A good cook is often a more successful therapist than the physician and in all instances is an essential auxiliary. In some febrile patients, anorexia, nausea and vomiting are pronounced and when these symptoms exist I know of no other condition that will so try the skill, resourcefulness, temper and perseverance of the physician.

When the time has come for the patient to leave his bed the vigilance of the physician must be doubled. At first he should be allowed to sit up for half an hour every alternate day, then each day, then twice a day and in some such manner the time out of bed gradually lengthened. How quick the progression may be must be decided by the symptoms of the patient, by the temperature, the pulse rate, the appetite, the cough and the general feeling of well-being. Fatigue must be sedulously avoided. After a number of weeks or months the patient is finally brought to some such daily schedule as follows:

8 A. M.........Breakfast in bed.
8.30 to 9.15....Lie down quietly to rest.
9.15 to 10.00....Bathe and dress slowly.
10.00 to 12.30....Out of doors in reclining chair.
12.30 to 1.00....Preparation for lunch.
1.00 to 1.30....Lunch.
1.30 to 3.00....Lie down quietly to rest.
3.00 to 5.30....Out of doors in reclining chair.
5.30 to 6.00....Preparation for dinner.
6.00 to 7.00....Dinner.
7.00 to 9.00....Out of doors in reclining chair if weather permits, if not then indoors.
9.00............To bed.
10.00............Bed wheeled out of doors for the night.

If the patient has not the advantage of a porch or two rooms the change from indoors to out of doors must be imitated by opening and closing the windows. In order to be comfortable in cold weather patients must get into a warm room three or four times a day for short periods. Debilitated patients and elderly patients often suffer severely from the cold and for them the routine must be tempered.

In the daily routine suggested it will be noted that food is taken only three times a day. It is my experience that most patients do much better with three meals a day than with six. Occasionally, however, this is not so and some patients who find it difficult to take sufficient food to nourish them properly succeed better with intermediate nourishment. If milk and eggs are advised they may be taken at the end of the meal. Since most patients with tuberculosis lose weight it is usually desirable to restore at least what has been lost and putting on weight is one of the most satisfactory and encouraging signs of improvement. Vagaries of appetite is a difficult problem the physician has often to deal with. However, it is not more frequent in tuberculosis patients than in other similar groups of patients and hardly as common as in the group of undernourished neurotics. Every physician is familiar with the patients who on account of slight digestive difficulties gradually restrict their diet almost to a starvation ration. In other patients, undernourished from childhood on, the chief difficulty seems to reside in habitual undereating, faulty habits acquired by indulgence and oversolicitous attention in childhood. These patients must be treated by a mixture of firmness and encouragement. Nothing is ever accomplished until the family is banished and a skillful, competent nurse is put in charge of the situation.

When such a routine is once successfully established the physician must pause there for an indefinite period. How long this period should be must be decided in each individual case. The progress of improvement is one deciding point, but the temperament of the patient, his financial situation, the character of his work, the demands made upon him and innumerable other extramedical considerations must have their due influence. I can only say that from the purely medical standpoint those who remain longest at this period are the most likely to arrest their disease. Naturally when a patient feels well he chafes at inaction. If the physician wishes to prolong the period of rest half the battle is won if he has been able to interest the patient in some quiet occupation that keeps him busy and engages his attention. Such occupations are now being generally devised and in many locations teachers devote themselves to instructing patients in what is justly called occupational therapy.

When the time arrives to begin exercise the physician has reached the third critical period in the course of treatment. The patient must now very gradually be prepared to return to his accustomed life. At first a short ride may be allowed or a slow walk of five minutes on the level every second day. Later the exercise may be taken each day, then twice a day, then the amount of exercise be gradually lengthened. Again the physician must be guided in his prescription by the condition of the patient, the temperature, the pulse rate, the appetite, the cough and the general feeling of well-being. *Fatigue must be sedulously avoided.* The least unfavorable symptom must be carefully looked for and should it appear the program is to be at once radically altered. Never wait to be convinced that exercise is doing harm but act immediately upon a suspicion that it may be doing harm.

Finally the time arrives when the patient returns home from the sanatorium or health resort, or, if he has been treated at home, when he is to return to work. This is the period of greatest danger and unfortunately guidance through this period is often placed in uncertain and inexperienced hands. It is the time when a recurrence of symptoms, a relapse, is most to be feared. Relapse occurs so frequently that the notion is prevalent that a patient treated away from home may never safely return. The physician charged with the care of a patient at this hazardous stage must have clearly in mind the danger that is run. On the surface everything has the appearance of bright promise. The patient returns to happy friends, robust in appearance and all obvious signs of the dreaded infection gone. It is hard for the physician not to enter whole-heartedly into the spirit of confident rejoicing and to ignore the possibilities of danger. Yet just when the promise is most alluring, the danger also is the greatest. The physician may be encouraged in his unpleasant task of warning mentor by the well-established fact that the longer the time that has passed after recovery the less is the chance of relapse. If the patient passes safely through the first year after recovery the danger of relapse is less than it was a year before; after two years is less than after one; after three less than after two and so on. This observation must stimulate us to put forth our best efforts during the first year that the patient returns to his accustomed life.

In the instance of men the first question to decide is what work and how much work the patient may do. There is as yet no clear evidence to show what occupations are good for tuberculous patients and what occupations are detrimental. We must appraise them upon the general principles that guide us in treatment. Since the treatment for tuberculosis is rest, fresh air and good food, so the ideal occupation is work carried out with little physical effort in the open air and yielding sufficient reward to insure freedom from financial care and a happy, bright, airy, comfortable home with a bounteous table. Needless to say such an occupation does not exist and endless compromise is demanded when we attempt to fit an actual job into such an ideal category. For the wealthy or even the moderately well-to-do the problem is relatively simple; for the artisan and the laborer it is excessively difficult.

As in treatment we put chief emphasis upon rest, so also in judging an occupation the physical effort demanded requires the most important consideration. Experience confirms this opinion, for tuberculous patients do better at restful work, even though confined, than they do at labor demanding much physical exertion even though carried out in the open air. Formerly when fresh air was considered the most important feature of treatment it was customary to advise tuberculous patients to seek an out-of-door employment. Nearly all out-of-door employment entails hard physical labor and most of such positions bring in scant financial reward. A patient is therefore subjected to physical stress to which he is unaccustomed and must at the same time live more economically—two conditions that react unfavorably upon his disease. The folly of such advice was soon learned and at the present time the tendency is to allow patients to return to the kind of work to which they are accustomed and for which practice has given them an aptitude. No one would now think of suggesting to an office employee that he go upon a farm. He is very fortunate to have acquired experience in work that demands so little exertion. Of course he should choose, if choice there be, a clean, well-lighted, well-ventilated office, but even though the office has none of these advantages still he is better off in a stuffy office than at hard work out of doors. Professional men will naturally continue to practice their profession. For instance, what else could a physician do but practice medicine? Artisans should with few exceptions return to the trade they have learned.

To seek another kind of employment means usually to engage in harder work for less pay.

It is a great advantage if the patient can begin his work with short hours and gradually come up to a full day. Whenever possible he should lighten his work and avoid getting into tight places from which he can extricate himself only by weeks of physical and nervous strain. He must sacrifice some of his ambition, if ambition drives him too hard. But whatever arrangements are made for his work he must understand absolutely that all other hours must be devoted to a consideration of his health. Many men work, and even work hard, and get well of tuberculosis; but very few indeed work and play and get well of tuberculosis. For the first six months the patient returning to work should devote all his hours away from work to a routine not less exacting than the routine he practiced while "curing." If his hours of work are from nine to five he should return home immediately after and go to bed and remain there until time to arise the following morning. It is an advantage to have the evening meal in bed. Sundays and holidays should also be spent in bed. I have known patients who for years have gone to bed each Saturday at noon and remained there until Monday morning. Such week-end periods of rest are invaluable. Only after months have passed may an occasional evening out be permitted. By such strict methods as these are patients slowly brought to recover their lost health. As years pass by and security becomes more firmly established they may gradually slip into more accustomed ways of living. If they are wise they will always remember the lesson so laboriously learned and never risk recurrence by rash and unnecessary exposure.

Every practitioner knows that the recovering tuberculous patient suffers relapse chiefly from two causes: from overexertion or strain and from acute respiratory infections. Up to this point I have spoken only of protection from strain and in reading over what I have written I get the dissatisfied impression that I have treated this side of the matter in a somewhat too mechanical vein. Perhaps what I have said in the introductory remarks may partly compensate for this one-sided presentation. However, no harm will be done by referring briefly again to a broader viewpoint. Rest, absence of fatigue and strain, has been presented as the very foundation of tuberculosis treatment, in the sanatorium, at the health resort and in the home, during the period of active symptoms and during the long after-period of convalescence. It is simple enough to rest the body and spare the muscles. It is not so easy to rest the individual. Even though the muscles be spared, a patient may be undone by worry, care, discouragement and vice. Spiritual and moral forces are almost as potent for good or for harm as are bodily rest and fatigue. Still, even though we freely recognize the important part they play, it is impossible to set down any definite rules by which we may control their action. All one can do is to point out their importance and encourage the physician to give them deserved consideration. Every patient is a new and difficult problem that must be studied with care and human interest. After the diagnosis has once been made, a sympathetic study of the personality of the patient and the environmental factors that play upon him is far more important to successful treatment than further careful study of the lungs. Conditions that will delight one patient will sour and depress another; work that will fill one with healthful interest and enthusiasm will leave another bored and irritated; recreation that will stimulate and refresh one will tire and fatigue another. All successful practitioners take these matters into account almost instinctively, but interest and experience may cultivate an appreciation of their value and enlarge the field of useful application. It is well to remember that in most instances who gives the medicine is more important than the medicine given.

During the period of active treatment it is usually easy to protect patients against prevalent respiratory infections. Physicians must be aware of the danger and exercise necessary precaution. Patients may be out in any weather provided chilling be guarded against. With reasonable care this may be ignored as a cause of colds. The important source of danger is contact with persons harboring such infections. Attendants, members of the family and visitors must be repeatedly warned against the danger. A thoughtless breach of instructions may cause the patient much discomfort and real harm. When a routine social life is resumed, protection from infection is more difficult. The patient must be instructed not to shrink from inclement weather but to dress properly for it. Risk of contact infection may be lessened by avoiding as far as possible crowded public places and conveyances and close association with those infected. Should the patient be so unfortunate as to contract an acute respiratory infection, he should go to bed immediately upon the appearance of symptoms and remain at rest until the symptoms have disappeared.

I have intimated that doubtful or commonly called suspected cases of pulmonary tuberculosis require special consideration from the standpoint of treatment. In these patients for one reason or another pulmonary tuberculosis is strongly suspected but the diagnosis cannot be established definitely upon firm evidence. Certain links in the chain of evidence are wanting and yet the facts discovered are circumstantially more or less convincing. Instances of this kind are extraordinarily frequent in the practice of every physician and they are puzzling from a therapeutic as well as from a diagnostic standpoint. They parade under various names according to the special interests and predilections of the physician. One, interested particularly in tuberculosis, makes a diagnosis of pulmonary tuberculosis and sends the patient off to a sanatorium from which he returns after months of rest a satisfactory testimonial to the good judgment of his physician. Another, interested particularly in gastro-intestinal disorders, will diagnose enteroptosis and put the patient to bed with elevated feet and furnish a liberal diet and, as weight is gained, the patient's improvement is equally satisfactory. Still another, interested particularly in neurology, may diagnose psychoneurosis and neurasthenia and institute a rigid rest and isolation cure, the while purging the mind of deadly repressions and vicious complexes, with results no less gratifying. And lastly the internist will recognize constitutional inferiority and the results of faulty training and he also will rest the patient, institute building-up measures and correct faulty habits with similar success. It will be noted that the fundamental part of treatment is the same in all instances and the results are therefore equivalent even though the details of treatment may vary and the diagnoses differ.

In doubtful cases of tuberculosis the physician has a long list of available and efficient therapeutic measures from which to choose. This choice must be guided by a consideration of all the individual and peculiar circumstances that surround the suspected patient and the effect that readjustment of these circumstances may have upon his personal development and his social relations. It is no light matter to draw the head of a family from his economic position and by long absence jeopardize his earning capacity. The mother of a family may not easily be spared from the home. Too solicitous care of an adolescent may seriously interfere with proper moral and intellectual development; and health, that might equally well have been preserved by more conservative measures, may be paid for by the cultivation of indolent and shiftless habits that quite unfit the adult for a useful station in life. These considerations are not fanciful, they are real; and a physician should carefully weigh all the immediate and remote consequences of his advice before urging radical measures.

Children predisposed to tuberculosis should be especially guarded. Their habits of eating, sleeping, playing and working should be regulated according to well-established hygienic principles. Proper hours of rest should be insisted upon and their vacations should be judiciously planned. Particularly should they be guarded against the overexertion of violent school athletics. Frail delicate youths are often urged to exercise themselves into proper development and robust form. The physician must guard against such ill-advised folly.

Suspected adults whose circumstances easily permit the diversion may be sent off to appropriate health resorts for rest and recreation. Even these must be warned against excessive athletic feats. The tendency is real and unless carefully instructed they are likely to overdo. However, the majority of doubtful cases must stay at home and the situation can be satisfactorily managed in a conservative way provided sufficient attention be given to details. In the first place, the physician must be sure that the disease is only suspected and not demonstrably present, that every diagnostic aid has been employed. Once assured he must then follow the patient at regular intervals, always watchful for the symptom or sign that will change his suspicion of disease to a conviction of its presence. Protected by such vigilance he may safely proceed to rearrange the patient's habits of life. The variations that may be employed are endless. Among others may be mentioned shorter hours of work, brief periods of rest during the day and in the late afternoon, to bed immediately after dinner five nights during the week, week-ends spent in bed, short vacations from work spent chiefly at rest. The program should be arranged by the physician and patient, and after adoption should be rigidly followed. The program will be varied, that is, made more rigid or relaxed, according to the improvement that occurs. That the plan may be followed by success the physician must give his orders specifically in writing. In all of my experience I have never seen a patient benefited to the slightest degree by such loose advice as "you must go slower and get more rest," whereas I have seen the greatest benefit result from the simplest readjustment of living habits definitely and concretely enjoined and faithfully carried out.

It has often been said that tuberculosis treatment can succeed only when the patient has enough brains to profit by advice and enough money to put it into practice. There is much truth in this saying. To carry on faithfully through long years of treatment requires determination and courage and cheerfulness to a high degree. A reasonable measure of intelligence is necessary to comprehend the aim and purpose of treatment and to draw support from this understanding. At the same time enough money must be at hand to assure the necessary comforts demanded by treatment and freedom from financial worry and care. Without this much money the treatment of tuberculosis is unfortunately seldom successful. Improvement at the sanatorium is almost certainly followed by relapse if the patient returns to conditions under which it is impossible to follow the instructions there learned.

Symptomatic Treatment

As we have already seen, it can hardly be sufficiently emphasized that the main reliance in the treatment of tuberculosis must be placed on hygienic measures. As a general rule, when the patient is treated with fresh air, a wholesome diet, properly regulated rest and exercise, all symptoms will soon be greatly ameliorated or disappear entirely. In such cases no especial treatment of symptoms is necessary, and patients do better without any such. In other cases, however, it may be found that one or more of the symptoms or complications of the disease is particularly exaggerated or unusually persistent, or even of the nature of a distressing emergency likely to endanger the life of the patient. In these cases especial measures directed toward the relief of such symptoms may be called for. The commoner symptoms and complications with the appropriate treatment for each will, therefore, be considered in the following pages.

Cough.—Cough is due to a reflex nervous stimulation, arising, in the great majority of instances, from somewhere in the respiratory tract. It is important to determine, as an aid to treatment, the location from which the reflex arises. While a "stomach cough," due to stimulation of the vagus endings in the stomach, is spoken of by many authors and is theoretically a possibility, it hardly deserves serious consideration, and is mentioned here only because it is far too frequently used by physicians as a convenient shield behind which may be found shelter from the necessity of telling an unwelcome truth to patients. Abnormal conditions in the ear, such as impacted cerumen, or in the nares, such as spurs or polypi, may rarely cause cough. An elongated uvula is another occasional cause. All such conditions should, if possible, be corrected. Much more common are the pharyngeal causes, a chronic pharyngitis often producing a persistent, irritating cough. This when found should be treated, preferably by alkaline sprays and by applications of silver nitrate solution (2 to 10 per cent), or iodin solutions. Laryngitis, also, either simple or tuberculous, is a common cause of cough which can often be lessened by appropriate local treatment (see preceding subdivision). Pleurisy may cause a most distressing cough, which can be greatly relieved by immobilizing the affected side with adhesive plaster.

But by far the commonest seat of cough in pulmonary tuberculosis is to be found in the trachea, bronchi, and bronchioles. The irritation may be produced either by the collected secretions, or by the inflammatory process. Sudden circulatory changes, such as are produced by arising from the horizontal to the upright position, or vice versa, or by the sudden change from a warm room to the cold outside air, tend to increase this irritation and may give rise to severe paroxysms of cough. Such sudden changes, when found to exaggerate coughing, should be avoided as far as possible. The pulmonary congestion caused by mitral disease is also productive of cough, and may occasionally be present as a complication of tuberculosis.

Two varieties of cough should be carefully differentiated: first, the dry, hacking, *unproductive* cough, out of all proportion to the amount of expectoration; and, second, the loose, easy, *productive* cough, which succeeds with little effort in raising the more or less abundant expectoration. It is important, when considering treatment, to make a distinction between these two, since the first is unnecessary and harmful, while the second is of benefit in ridding the respiratory tract of its collected secretions. A little questioning or observation of the patient will soon enable the physician to determine to which of these varieties the cough belongs, and so to form an opinion as to the desirability of attempting to suppress it. In general, it may be said that the drier and more unproductive and more violent the cough the more active should be the means taken to prevent it. It is a most important point that those coughs which necessitate a considerable expenditure of energy should by some means or other be controlled. If simple measures will suffice, so much the better; but, if not, then sedative drugs are the lesser of two evils and should be resorted to.

We may for convenience make four classes of the means at our disposal of controlling cough: (1) prophylactic, (2) suppression, (3) local measures, and (4) sedative drugs.

Prophylactic Measures.—The patient should be instructed to avoid those acts which by experience have been found to provoke severe cough. Too much or too violent exercise may be a cause, especially if carried to the point of breathlessness. Loud talking, laughing, or singing may be factors. Getting chilled, exposure to severe winds, a sudden change from breathing warm air to cold air—any of these may be found to excite paroxysms of cough, and, if so, should be avoided. The cough produced by change of position has been mentioned. Inhaling dust, smoke, or irritating vapors of any kind is apt to be a cause. Tobacco smoking comes under this head and may have to be forbidden. Especially annoying is the cough that comes after taking food, sometimes provoking vomiting. A hot drink shortly before meals, a soft, non-irritating diet, the thorough mastication of the food, and care in not overloading the stomach may overcome the difficulty, but occasionally the vomiting is so persistent as to lead to malnutrition, and in such cases a sedative, preferably codein or heroin, must be given shortly before the meal.

Suppression of Cough.—This is the most important of all points in the treatment of cough. The physician should explain to the patient that all hard coughing is not only unnecessary, but is positively harmful, and should urge and insist that, by force of will power, he refrain from coughing until absolutely compelled to do so. This requires a somewhat unpleasant effort at first, but the patient who persists in refusing to yield to the impulse to cough will soon be rewarded by finding that the impulse becomes much less, that the cough is easily controlled, and that the expectoration, when ready to come up, will do so with little effort. The very act of coughing, by increasing the irritation in the respiratory tract, increases the necessity for coughing, and a vicious circle is soon formed. A convenient analogy for explaining this to the patient is that of the mosquito bite. If the desire to scratch be controlled for a few minutes, the irritation and inflammation subside; but, if the desire be indulged, instead of relief there is an aggravation of the condition. In this matter of suppressing a cough there are various little expedients that may help. A few long, deep breaths, or holding the breath, may be tried. Sips of cold water or bits of ice are often efficacious.

Local Measures.—If the above measures are unsuccessful, recourse should next be had to local measures for allaying the irritation in the respiratory tract. Small quantities of demulcent substances, such as mucilage of acacia, glycerrhiza, slippery elm bark, Iceland moss, or the old-fashioned linseed or flaxseed tea may be tried. Mentholated lozenges, allowed to dissolve in the mouth, are sometimes of value. All such remedies should be used with moderation lest they upset the digestion. Milk possesses demulcent properties, and often sips of hot milk will accomplish as much as any of the above-mentioned drugs, and with no damage to the digestion. Spraying the throat with a 2 per cent solution of menthol in albolene is sometimes efficacious. Any of these remedies may be found to give great relief when the source of irritation is in the pharynx or upper part of the larynx. When it is lower down they are valueless. In such cases inhalations may accomplish the purpose. A very satisfactory one is the following:

℞

Creosote (beechwood)	6 per cent
Menthol	2 per cent
Oil eucalyptus	12 per cent
Tinct. benzoin co.	80 per cent

A teaspoonful of the mixture should be added to a pint of boiling water in an inhaler or croup kettle, and the vapor inhaled. Or the following may be used in the same way:

℞

Creosote	
Tinct. benzoin co.	
Oil terebinth	āā 10 c.c. ʒiiss

Continuous inhalation of various drugs by means of a Yeo mask, or one of its modifications, has been warmly recommended by some authors, and may be tried if other methods fail to control the cough. Creosote is probably the best drug to use for this purpose.

Some patients seem to obtain relief from counterirritation over the trachea or bronchi. Tincture of iodin or a mustard plaster may be tried in this way.

Sedative Drugs.—If prophylaxis, suppression, and local measures fail to control the cough, sedative drugs become necessary. The harm of violent exhaustive cough certainly outweighs the harm such drugs may do. There is little objection to their use in far-advanced cases, but in early cases they should be used only when other measures fail. They are of especial value in the severe paroxysms of coughing occurring during the night and preventing sleep. As has been mentioned above, they may also be serviceable in the persistent cases of cough accompanied by vomiting. In cases complicated by laryngeal tuberculosis they should be resorted to as the lesser of two evils, in order to save the larynx from the severe wear and tear produced by coughing. After hemorrhage they should be used without hesitation when there is any tendency to racking cough. Of the drugs to be used codein, from ⅛ to ½ gr. (0.008 to 0.032 gm.), or heroin, gr. 1/24 to 1/6 (0.003 to 0.010 gm.), are most satisfactory. Either one, if continued very long, will lose its effect, when the other may be substituted. The elixir of heroin and terpin hydrate in teaspoon doses is more efficient in some cases. Severe paroxysms of cough, evidently sapping the patient's strength and throwing violent strain on the heart and circulation, may be controlled by a few inhalations of chloroform. Only in moribund cases, and when all other measures fail, should morphin be used as a remedy for cough, on account of the danger of forming the habit.

Expectoration.—Changes in the amount and character of expectoration afford an excellent index as to the progress in the lung lesions. If the lung condition is improving under hygienic treatment, there is usually a considerable decrease in the amount of expectoration. Ordinarily no especial measures should be taken to reduce the amount. If it is excessive or is increasing, it is inadvisable to allow the patient exercise. In case of a sticky, thick, tenacious sputum, difficult to raise, it may be advisable to use expectorant measures. A glass of hot water is sometimes very effectual. Either of the steam inhalations mentioned under the treatment of cough may be tried for this purpose, often with marked benefit. Of drugs, ammonium chlorid, gr. 5 to 10 (0.3 to 0.65 gm.), is probably the best. Its use alone should not be long continued, on account of the danger of causing gastric disturbance. Profuse expectoration may be in some cases caused by secondary organisms. In these cases creosote or one of its derivatives will sometimes be found to have marked value in lessening the amount of the expectoration. It is best given well shaken in an ounce or two of *hot* water, about an hour after meals. Small doses (1 or 2 minims—0.065 to 0.120 gm.) should be used at first, and this increased a drop or two at a time up to 10 or 15 drops three times a day. The heroic doses sometimes advocated are to be condemned. Large doses have a tendency to upset the digestion, and this counterbalances any possible benefit as a pulmonary disinfectant. It is best to discontinue the drug at once; later, perhaps, to resume it again with smaller doses, if the patient complains of its causing digestive disturbance. Numerous derivatives of creosote have been introduced, guaiacol carbonate, creosotal, gomenol, etc., but they seem to have little advantage over the pure creosote.

Hemorrhage.—This symptom is the *bête noir* of both patient and physician. The suddenness of onset, the sight of blood, the choking sensation, the inaccessibility of the bleeding vessel to direct treatment, the dread of a fatal outcome, all these can hardly fail to have a depressing effect on the patient. In no other symptom or event is the rôle of the physician so important or his presence so necessary. Much depends on getting the patient quiet, both physically and mentally, as soon as possible. It is remarkable how soon a hemorrhage will sometimes stop as soon as the patient's mental anguish and intense anxiety are put to rest by the presence or reassuring words of a calm, self-possessed physician or nurse.

Hemorrhage varies all the way from a blood-tinged sputum to a loss of blood so excessive that the patient succumbs in a few minutes. The cases of blood-streaked sputum require no other treatment than the refraining from exercise until the sputum is clear, and the prophylactic measures suggested below. All cases in which there occurs a spitting of pure blood should be placed in bed and treated in accordance with their severity until the bleeding has ceased, and the danger of recurrence is past.

The first thing to be done in case of hemorrhage is to get the patient to bed. He should lie flat on his back, a pillow may be placed under his head if more comfortable, and his head turned to one side to facilitate the expectoration of the blood. He should not be allowed to talk or to use his arms, or to raise his head in order to expectorate, but the attendant should hold a basin or sputum cup to catch the blood, and should wipe it away with pieces of gauze or linen as it accumulates in the mouth of the patient.

If the patient is frightened or nervous the physician should endeavor in every possible way to reassure him, since nervousness and emotion raise blood-pressure and thus are a contributory cause of hemorrhage. Unless this is sufficient to accomplish the purpose, morphin should be used without hesitation. It is best given hypodermatically in doses of 1/8 to 1/4 gr. (0.008 to 0.016 gm.), and may be repeated if necessary. Besides quieting the patient and reducing blood-pressure, it also has the valuable effect of allaying the cough, which is a dangerous factor.

An ice-bag applied over the heart also has a good effect in quieting the heart action and so reducing pressure. Some advise the application of cold over the supposed site of the bleeding vessel. As this is a point usually impossible to determine, since it is decidedly dangerous to attempt any but the most superficial examination while the hemorrhage is in progress, the measure is one of very doubtful efficacy.

Various drugs have been advocated; only a few deserve mention. As hemorrhages tend to stop spontaneously as soon as the decreased quantity of blood in the vessels has lowered the pressure and shortened the coagulation time, it is hardly accurate to attribute the favorable result to the particular drug used at the time. As a routine measure the use of drugs, except morphin, for controlling pulmonary hemorrhage undoubtedly does more harm than good. Salt is a household remedy, but there seems to be no reason for its use, and it may excite gastric disturbance. Intravenous injection of 5 to 10 c.c. of a hypertonic salt solution (10 per cent) in some cases is effective, apparently increasing the coagulability of the blood. Ergot and adrenalin, from the fact that they are known to control hemorrhage in other parts of the body, have been advocated. The evidence offered in support of either is hardly convincing. Both of them raise pressure in the systemic and so indirectly in the pulmonary circulation, exactly the thing to be avoided if the clotting is to take place. In cases of continued slow oozing of small amounts of blood they do at times appear to be of value.

On the other hand, the nitrites, or pressure reducers, do influence some cases favorably. It is well to control their administration by blood-pressure estimations at frequent intervals. If the pressure falls below 120 mm. they should be discontinued. At the beginning amyl nitrite is of the greatest value on account of the rapidity of its action. A pearl of amyl nitrite should be broken in a handkerchief and inhaled, if the pulse feels hard. Since its action is as transitory as it is rapid, it should be followed by nitroglycerin, gr. 1/100, or sodium nitrite, gr. 1, of which the effects are of much longer duration. The dose may be repeated every three or four hours if the pressure still remains high. Erythrol tetranitrate, gr. ¼ to 1, often acts better than either of the above, and in many patients seems less apt to cause gastric disturbance and headache.

It is also advisable, in the case of continued or repeated hemorrhages, to make a determination of the coagulation time of the blood. If this is much prolonged, which happens but rarely, calcium lactate, gr. 15 to 20 (1.0 to 1.3 gm.), should be given three times a day. Gelatin, either by mouth or subcutaneously, has also been recommended. Horse serum, subcutaneously in doses of from 20 to 40 c.c., is sometimes used with the same object in view. It may give rise, however, to disagreeable skin eruptions or other anaphylactic phenomena, especially if the doses are repeated.

In severe hemorrhages the application of ligatures to one or more of the limbs is a measure worthy of trial. The ligatures should be tight enough to restrict the venous, but not the arterial, circulation. In releasing them one should be careful to allow a considerable interval after the removal of each ligature, in order that too great a quantity of blood may not be admitted into the circulation at once.

Following a severe hemorrhage nothing should be given by mouth for several hours, except a little cracked ice, or occasional sips of water if there is thirst. As long as any bleeding persists the diet should be restricted. The greatest danger seems to be in overloading the gastro-intestinal tract with either fluids or solids, and so throwing an extra burden on the circulation. The most rational plan would seem to be to diminish proportionately the quantities of both fluids and solids that constitute the patient's ordinary diet, the amount of restriction varying with the severity and persistence of the hemorrhage. It is better to allow small quantities of food at more frequent intervals rather than to give any large amount at one feeding. Alcohol, tea, and coffee should be prohibited.

It is important that the bowels be kept freely open. Violent purging, on the other hand, may be harmful on account of the frequent strain in the act of defecation. Laxatives, such as cascara, compound licorice powder, or a pill of aloin, strychnin and belladonna, may be given each night, and enemata used if these are ineffectual.

According to Billings emetin hydrochlorid gr. ½ to 1, given hypodermatically, has been found to stop hemoptysis. It may be repeated in four hours. The *modus operandi* is not known, but the result is very satisfactory.

As to the after-treatment of hemorrhage, this will vary much with the severity of the case. After a small hemorrhage, that is to say, one or two mouthfuls of blood at the outset, the patient should always be kept in bed for one or two days and then, if the sputum is clear and temperature normal, he may gradually be allowed to resume his usual life. After larger hemorrhages he should be kept in bed and under close observation for several days. The greatest danger from hemorrhage is not the anemia and prostration from loss of blood, but the chance of the extension of the diseased area or even the production of a pneumonia from the blood aspirated. Symptoms of such a complication should be carefully watched for. A rise of temperature following hemorrhage is not at all uncommon, and is probably due to absorption of blood. Such a temperature should subside within a few days, and any persistence of it should lead to the suspicion of renewed activity of the tuberculous process. Without such a complication the loss of blood, even from a large hemorrhage, is soon repaired, and in many cases the patient seems none the worse. A tonic of iron or arsenic or small doses of strychnin may be of service during this stage of repair. Immediately following large hemorrhages, if there are symptoms of shock from loss of blood, salt solution by rectum, or better by hypodermoclysis, should be administered. With patients subject to hemorrhage much may be done by prophylactic measures. Such patients should avoid any violent exercise, loud laughing, shouting, or singing. Tea, coffee, or alcohol should be used sparingly, if at all. Overloading the stomach or, in fact, excesses of any sort should be avoided. On the appearance of blood-streaked sputum such patients should go to bed and remain there until all traces of blood have disappeared.

Gastro-intestinal Disturbances.—These are common among tuberculous patients, though becoming less so as the practice of forced feeding is abandoned. Most patients still hold more or less firmly the conviction that "stuffing" is an essential in the cure of tuberculosis. So firmly has this notion become rooted in the minds of the laity that the physician with modern dietetic ideas is apt to meet with considerable opposition, open or secret, when he attempts to enforce them. Undoubtedly many of the stomach and intestinal symptoms complained of by patients are due to such "stuffing," either in the past or present. Anorexia, flatulence, constipation, diarrhea, nausea, and vomiting, or abdominal pain are the symptoms most commonly met with. When a patient persistently complains of one or more of these symptoms the first important point to determine is the nature and amount of his diet. The methods for doing this and the proper dietary for tuberculous patients are considered elsewhere in this article. If the patient is found to be greatly exceeding this normal requirement, a simple reduction of the amount eaten will often clear up the symptoms. An excess of proteid, even though the total amount of food be not in excess, is often productive of gastro-intestinal disturbance. In this case the patient should be instructed to eat more carbohydrate and less proteid, or, in plainer words, more cereals, bread, and vegetables, and less meat and eggs. Sometimes a patient will be found to be eating excessively of one particular article of food, especially milk or eggs or meat, and in such case a simple curtailment of the amount of these articles may be found sufficient. If after these corrections in the diet symptoms still persist, a more serious impairment of digestion or possible organic lesions in the intestines should be suspected. Of the various tests which have been proposed or used for testing the intestinal functions, the most satisfactory is that of Adolph Schmidt. Simply stated, this method consists of the careful examination of the feces obtained after a test diet. The test diet used at the Loomis Sanatorium modified slightly from the one described by Schmidt is as follows:

Breakfast.—One soft-boiled egg; two slices toast with butter; one bowl of oatmeal, strained, with sugar and cream; one glass milk; one cup coffee (if desired).

Dinner.—One-quarter pound finely chopped round steak (slightly broiled); one-half pound mashed potatoes; two slices of bread or toast with butter; one or two glasses of milk.

Supper.—Same as breakfast.

This diet is easily digested by normal persons, furnishes a sufficient number of calories to meet the nutritional requirements of the body, and contains the proper proportion of proteid, fat, and carbohydrate. The diet is given the patient for three days, or until certain that the feces are coming from it. It is well to give a charcoal tablet with the first breakfast, note the time which elapses before the black appears in the stools (which furnishes a rough estimate of the mobility of the gastro-intestinal tract), and then to continue the diet until the black has entirely disappeared before selecting a specimen for examination. The stool is first examined macroscopically for mucus, blood, pus, parasites, etc., and then a small portion finely ground in a mortar is pressed between two glass plates and inspected for any abnormal constituents or undigested food remains. Normal stool from the test diet should be homogeneous, with no remains of undigested food. In abnormal conditions one may detect after a little practice connective tissue, muscle, potato, or fat remains, or mucus flakes. Next, a microscopical examination should be made, by which the macroscopical is confirmed, and undigested muscle fibers, starch cells, or fat detected. A few chemical tests should also be made, that is, the reaction to litmus, the sublimate test for bile, and the incubator test for gas formation. In the latter test a small amount of feces is placed in a special fermentation tube, allowed to incubate at 37° C. for twenty-four hours, and then inspected to determine the formation of gas. Gas formation, unless very slight, is pathologic. It may be due either to putrefaction or to fermentation changes. If the former, the reaction will have become more alkaline; if the latter, more acid than it was originally. Finally, smears should be made and examined for tubercle bacilli.

By following this method carefully very valuable information can be obtained as to the nature of the digestive disturbance. Enteritis or colitis may be diagnosed by the presence and character of mucus or pus. If these lesions be tuberculous, there will usually be found large numbers of tubercle bacilli in the mucus or throughout the stool. A diagnosis of intestinal tuberculosis should not, however, be made on the presence of tubercle bacilli in an otherwise normal stool, since there is always the possibility that they may have been swallowed, or even that they may be non-pathogenic acid-fast organisms.

Functional disturbances of digestion may also be diagnosed with the aid of the diet. Undigested connective tissue remains are held by Schmidt to indicate impaired gastric digestion. This diagnosis may be confirmed by the use of the stomach tube for gastric analyses. Administration of dilute hydrochloric acid will often materially help this condition.

Intestinal indigestion is to be diagnosed when an excess of fat, muscle fibers, or starch is found. A fermentative intestinal dyspepsia is not uncommon among tuberculous patients, showing itself clinically by the symptoms of flatulence, colicky pains, and often diarrhea, and in the feces examination by the presence of starch granules (recognized macroscopically by their reaction with iodin), acid reaction, and gas formation. This form of indigestion can often be materially benefited by giving a carbohydrate-free diet for a few days, followed by a gradual return to a normal diet, or to one in which the carbohydrates are restricted.

Insufficiency of proteid digestion in the intestine is shown by the presence of muscle fibers, sometimes associated also with putrefactive changes. Flatulence and diarrhea may also be present in this form. This type can be benefited by a diet in which the proteid is restricted. Meat should be used very sparingly, if at all, and the proteid necessary to maintain nutrition taken in the form of milk and vegetable proteids. Lactic acid bacilli, in the form of buttermilk, are also of value when there is putrefaction.

If thorough feces and stomach tests are negative, if abdominal examination reveals nothing abnormal, if a diet proper as to quantity and composition is being taken, and yet, in spite of the apparently normal condition, the patient continues to complain of symptoms referable to the digestive tract, then the trouble is in all probability purely mental. A thorough explanation of this fact should be given to the patient, and then every effort made to get his attention away from the digestive tract. Drugs should not be used in this condition, as they serve to keep the attention on the digestion.

Anorexia.—This symptom, so common in tuberculosis, is probably due to the toxemia of the disease. As the latter is reduced under treatment the appetite usually improves greatly. A bitter tonic, such as nux vomica, strychnin, or gentian, before meals, or small doses of alcohol in the form of wine, beer, or ale with the meals, will often stimulate a flagging appetite and enable the patient to consume a normal quantity of food. If the anorexia and repugnance to food are so great that the patient can eat very little at one time, it is well to give frequent small feedings, one every two hours, for instance, of easily swallowed foods, such as milk, raw eggs, beef juice, albumin water, soft toast, etc., rather than attempt the ordinary three large meals. The patient will usually succeed in taking more food with less trouble by this method.

Constipation.—The treatment of this troublesome complication does not differ from that in the non-tuberculous, except that it is more important that it be not neglected. A dose of calomel and salts often clears up surprisingly, for the time being, the headache, lassitude, and general depression associated with a sluggish bowel. If a constant laxative is necessary, fluid extract of cascara sagrada is as satisfactory as anything. Agar is very effectual with a few patients, but most tire of it.

Diarrhea and Intestinal Tuberculosis.—The acute attacks of diarrhea are best treated by a dose of castor oil, followed by bismuth subnitrate or subgallate in 20-gr. doses (1.30 gm.) every three or four hours, with a soft diet with boiled milk as its basis until the trouble is checked.

The diarrheas associated with fermentative or putrefactive intestinal indigestions have been considered above. An initial dose of castor oil and a few doses of bismuth are of advantage at the start, although the main reliance must be on proper diet.

Chronic diarrheas in the tuberculous are usually due to intestinal tuberculosis. Local treatment is very unsatisfactory. Occasionally, perhaps more often than we suspect, intestinal lesions clear up under hygienic treatment. When the symptoms are pronounced and persistent, however, there is little to be hoped for, and palliative treatment is all that is left us. A soft diet sometimes gives relief. Some patients seem to do better on a diet in which the fluids are restricted. Fruits and green vegetables are apt to cause distress and may have to be prohibited. In most cases one diet seems to be about as good, or as bad, as another, and there is no harm in allowing the patient to have whatever he desires. Ichthoform, best given in capsules in doses of from 5 to 10 gr. three or four times a day, sometimes affords relief for a time. Bismuth often relieves the symptoms somewhat, but for the intense and constant abdominal discomfort characteristic of these cases opium usually furnishes the only means of relief. Colonic irrigations with silver nitrate (1: 5,000 solution) seem to have a palliative effect and may be tried.

Fever.—See Management During Stage of Active Process.

Night Sweats.—Like fever, these are a symptom of toxemia. The treatment should be directed against the cause instead of the symptom. As a rule, they clear up as the patient's condition improves without other treatment. If severe and persistent, there are certain palliative measures which may reduce the sweats and make the patient more comfortable.

It is important that the covering be not too heavy. Flannel nightclothes should be worn, and only sufficient blankets to prevent chilling. A thorough sponging with alcohol, 50 per cent, or vinegar and water at bedtime is a help. A cold compress to the chest is sometimes effectual. A glass of cold milk on retiring or when awake during the night seems useful in certain cases. One or two teaspoonfuls of whisky or brandy may be added to the milk or given separately at bedtime. Of other drugs camphoric acid, 15 to 30 gr. (1.0 to 2.0 gm.), given at bedtime, may be tried. Atropin, 1/200 to 1/100 gr. (0.0005 to 0.001 gm.), best given hypodermatically, is the most effective drug, and may be used in severe sweats in the late stages. It often causes an unpleasant dryness of the throat, and care should be exercised in its use.

Dyspnea.—The shortness of breath on exertion often complained of by patients who have been for some time on little or no exercise is of small moment, in the absence of other symptoms, and usually disappears as the exercise is gradually increased and the heart muscle thus restored to its proper tone.

In advanced cases, especially of the fibroid type, dyspnea may be a distressing feature, and is here probably due to lack of sufficient functionating lung tissue. Since the lung tissue cannot be restored, there is no cure for it. The patient should be warned against any overexertion.

The dyspnea due to extensive pleural adhesions often improves under graduated exercise. That due to a rapidly developing effusion or pneumothorax should have treatment directed toward those complications. Occasionally attacks of true bronchial asthma arise in tuberculosis, and here the treatment, unsatisfactory though it is, does not differ from that of the same condition in the non-tuberculous.

Finally, there remains the dyspnea of the last stages, due to a failing circulation, where treatment can be only palliative. Strychnin, nitroglycerin, or, more often perhaps, morphin frequently seem to give relief. Inhalations of oxygen sometimes conduce to the patient's comfort.

Pain in the Chest.—This is of frequent occurrence and varies from a dull, indefinite ache, through all gradations up to the excruciating knife-like pains of acute pleurisy. The origin of the pain is often difficult to determine, for it may be from pleurisy (either the rubbing of inflamed surfaces or the dragging on pleural adhesions), or from intercostal neuralgia, or from myalgia of the intercostal muscles. But, whatsoever the cause, the treatment is the same. If the pain is so slight as to cause little discomfort, it should be disregarded. If more severe, counterirritation should be used over the painful area, either a brisk rubbing with wintergreen or chloroform liniment, or the painting with tincture of iodin, or the application of mustard plasters. If these measures do not suffice, or in any case if breathing or coughing causes severe pain, the affected side should be strapped with strips of adhesive plaster. These should be applied at the end of forced expiration, and drawn as tightly as possible, so as to restrict to the greatest extent all motion of the chest on that side. In very severe cases of pleural pain hypodermics of morphin may be necessary.

Insomnia.—Not infrequently patients attempting to sleep out of doors find sleeping difficult, either on account of the unaccustomed noises, the increased light, the wind, or other novelties in their surroundings. Usually the condition rights itself after a few nights, but in very light sleepers this may not be the case, and they should then be advised to sleep in a well-ventilated but dark and quiet room. Those suffering from insomnia should avoid physical or mental excitement during the evening. A glass of hot milk at bedtime or during the night is often helpful. Of drugs, bromids, though not as effectual as the hypnotics, veronal, trional, paraldehyd, etc., are safer and less depressing and should be used first, provided the condition does not yield to simple measures.

Menstrual Disturbances.—Amenorrhea is a not infrequent symptom of tuberculosis. It is probably a conservative measure on the part of nature for curtailing any unnecessary expenditure of energy, and no treatment should be directed against it. Severe dysmenorrhea, menorrhagia, or metrorrhagia, if present, probably arise from other causes than pulmonary tuberculosis. If persistent an examination should be advised to determine if possible any local abnormality or pathological process.

Anemia.—This is usually more apparent than real, and a blood count and hemoglobin estimation should always be made before beginning treatment. If anemia is actually present, iron and arsenic should be administered.

Pleural Effusion.—There has been great difference of opinion as to the desirability of aspirating pleural effusions. The generally accepted procedure has been to aspirate any except very small effusions as soon as diagnosed. On the other hand, there is considerable evidence pointing to the fact that a moderate effusion is a beneficent, purposeful effort on nature's part to relieve the strain on diseased tissues. The effusion acts as a splint to the diseased lung, limiting its motion and allowing it needful rest. There is no doubt that many cases do show greater improvement both in general and local condition during the presence of an effusion. For this reason our method of late years at the Loomis Sanatorium has been, in the absence of cardiac or pulmonary distress, to allow a moderate or small effusion to remain until absorbed, and even to regard its presence with satisfaction. If, however, the effusion is so large as to cause respiratory or cardiac distress, or if the initial fever which so often accompanies its development does not after a few days subside, then aspiration of at least a portion of the fluid is advisable.

Empyema.—If signs indicate fluid in the pleural cavity and symptoms point to pus, a needleful of the fluid should be aspirated for diagnosis. If the fluid is purulent, thoracotomy should be performed and drainage established without delay.

Pneumothorax.—This, as is the case with effusion, is often a beneficial event. If, as sometimes happens, it is so extensive or of such sudden onset as to cause severe collapse, the patient should be kept at absolute rest and heart stimulants used if necessary. In these cases the attempt may be made to aspirate some of the air, though this measure is of doubtful efficacy.

Coryza and Bronchitis.—The common "cold" is not to be regarded lightly in the case of the tuberculous, for it often seriously retards the progress of a favorable case, or hastens the decline of an unfavorable one.

As prophylactic measures the wearing of sufficient clothing, varying according to the season, avoidance of overheated, "stuffy" rooms, and the daily cold sponging of neck and chest are important. At its onset a cold can sometimes be aborted by a hot foot bath, hot drinks, a dose of Dover's powder, and rest in bed in a warm but ventilated room. Small doses of atropin or belladonna sometimes afford relief. The salicylates, especially aspirin, are often of value, especially if there is general aching or discomfort. Aspirin may be given in 5 to 10-gr. (0.30 to 0.60-gm.) doses every three hours. For the stuffiness in the head and the clogging of the nasal passages spraying the nares by means of an atomizer furnishes the greatest relief. Adrenalin solution (1:10,000) may be used first, followed as soon as the hyperemia is reduced by an oil spray, the following being a good prescription:

℞

Menthol	gr. 10	gm. 1.0
Camphor	gr. 10	gm. 1.0
Eucalyptol	min. 5	gm. 0.5
Olei rosæ	min. 1	gm. 0.1
Alboleni q. s., ad.	oz. 1	gm. 50.0

Instead of spraying, a medicated ointment may be rubbed into the anterior nares and allowed to melt and run back through the nasal passages. The following may be used for such purpose:

℞

Boric acid	gr. 10	gm. 1.0
Menthol	gr. 2	gm. 0.2
Unguenti aquæ rosæ	oz. 1	gm. 50.0

The throat and nasopharynx should be sprayed with Dobell's solution at frequent intervals, if pharyngitis be present. Bronchitis is best treated by inhalations, either moist inhalations, such as described in the section on Cough, or by means of sprays from an atomizer nebulizer. A good prescription for the latter purpose is as follows:

℞

Menthol	gr. 20	gm. 2.0
Creosoti	min. 20	gm. 2.0
Olei eucalypti	dr. 4	gm. 25.0
Alboleni q. s., ad	oz. 2	gm. 100.0

Otitis Media.—This is not an uncommon tuberculous complication, occurring in 17, or 3 per cent, of 550 patients in all stages of the disease treated at the Loomis Sanatorium. Its treatment should be delegated to the aural specialist.

Tuberculous Abscesses and Fistulæ.—The most common seat of these is in the tissues about the rectum, but they also not infrequently occur in the chest wall. As soon as the presence of pus is diagnosed the abscess should be opened, irrigated, and drained. The abscess walls may be mopped with tincture of iodin diluted one-half with alcohol, a very efficient germicide and a stimulation to the production of healthy granulation. Old fistulæ may occasionally be cured by injection of Beck's bismuth paste (bismuth subnitrate, 33 per cent, in vaselin), and this should be given a trial, but for most cases the only radical cure is surgical excision. The general condition of the patient should be very carefully considered, however, before any operation requiring a general anesthetic is attempted.

Special Methods of Treatment

I have previously stated that rest of the tuberculous organ or tuberculous structure is an important part of treatment. In a measure recovery from tuberculosis will vary with the extent to which the affected part may be put at rest. Witness the results in tuberculosis of the bone and joints. This fruitful method of treatment has not been neglected in pulmonary tuberculosis. Its value has long been recognized. The beneficial effects of pleural effusion upon tuberculous lesions in the lung were commented upon a century ago. The relation is often striking. Concomitantly with the appearance of fluid, fever abates, cough and sputum decrease and the patient's general condition improves. Aspiration of the exudate may be followed by a recurrence of the previous symptoms, which again subside as the fluid reaccumulates. Occasionally even in advanced tuberculosis the advent of pneumothorax marks the beginning of improvement in the pulmonary condition. The symptoms of progressing disease abate, the patient's general condition improves and the signs of pulmonary involvement diminish.

The favorable influence of these accidents is reproduced by artificial measures. Many physicians have imitated the results, limiting the movements of the chest by mechanical measures. Denison, of Colorado, particularly, many years ago emphasized the value of unilateral immobilization of the chest by strapping. Webb has pointed to the benefit of using the simple expedient of lying upon the affected side to limit the excursion of the diseased lung. Sewall has devised a simple belt which when properly applied limits the movements of the upper part of the chest. Knopf believes the same result may be obtained by the practice of voluntary control of respiratory movements, learning gradually to breathe almost exclusively with the diaphragm. Each of these methods is a valuable adjunct to the treatment of pulmonary tuberculosis.

The striking improvement that sometimes follows the occurrence of pneumothorax led gradually to the practice of inducing pneumothorax as a deliberate method of treatment. This was first undertaken by Forlanini in 1882 and was independently employed in this country by Murphy in 1898. However, the method was not generally adopted until some years later and Brauer deserves the credit for giving it wide popularity through his studies and writings. During the past fifteen years induced pneumothorax has won a secure place as a valuable addition to our method of treating pulmonary tuberculosis.

Induced Pneumothorax

Selection of Cases to be Treated.—In spite of the extensive use to which pneumothorax treatment has been put there is not yet a clear, generally accepted group of criteria by which the choice of patients suitable for treatment may be directed. Some authors would have us treat only patients with unilateral disease; others are willing to accept those with both lungs involved. Some reserve this method of treatment as the very last resort; others urge that it be used while there is still some reasonable prospect of recovery. There are only two points upon which every one seems to agree; pneumothorax treatment should not be practiced upon patients with early pulmonary tuberculosis, nor upon patients with more advanced disease who are progressing satisfactorily under conservative methods of treatment. Except for the control of hemorrhage, pneumothorax is employed only when other methods of treatment have failed. To the inexperienced the reason for this may not be clear; indeed it is a direct contradiction to the hopes of Murphy, who anticipated that pneumothorax would prove to be especially valuable in early cases. If rest is advantageous then it is only reasonable to infer that the patient should have the benefit of this remedial measure at the earliest possible moment. Since in practice pneumothorax treatment is withheld at such a time, one is led to suspect that there are certain results of the treatment which are not desirable. And this suspicion is justified. When pneumothorax has been maintained for some time pleural effusion often develops. This pleural effusion may persist in spite of repeated tapping and prevent expansion of the collapsed lung. Fibrosis of the collapsed lung gradually develops and even in the absence of pleural effusion may prevent expansion of the lung when air injections are discontinued. In a word, if pneumothorax is maintained for any length of time there is danger that the lung may never again be able to expand and fill out the chest and function normally. When a lung is badly diseased and observation convinces that in spite of treatment the disease is spreading, one does not hesitate to risk permanent loss of the lung in trying to halt the disease. After all a person is better off with a fibrous nubbin than with an expanded lung riddled with advancing disease. It is surprising how comfortable one may be with only one functioning lung. I have seen a healthy boy, who for a number of years had had a complete pneumothorax that came on spontaneously, whose only symptom was breathlessness on exertion. For years I followed a young man with a hydropneumothorax that followed pneumothorax treatment. He led a very active life and complained only of shortness of breath on exertion and of the unpleasant sloshing about of the fluid in his chest. Many similar instances might be cited. However, in spite of this bright side to the situation, one would not lightly curtail one's functional range by giving up a lung. In addition to this functional sacrifice certain grave dangers menace patients with pneumothorax. Perhaps the gravest of these dangers might not exist if the collapsed lung were in a healthy state; I am inclined to believe it would not; but collapsed tuberculous lungs rupture and cause pyopneumothorax often enough to make the danger very real. There is also the further danger of an acute respiratory infection attacking the sound lung. Under such circumstances, as far as my knowledge goes, pneumonia is uniformly fatal. Therefore a patient with a permanent pneumothorax has a well-limited functional range and also faces the danger of complications that threaten life. One should not be willing to risk this permanent disadvantage and these ever-present hazards unless a still graver risk is run by withholding pneumothorax.

Although it is generally conceded that the treatment should be restricted to moderately advanced or advanced cases of pulmonary tuberculosis who are not progressing satisfactorily, the selection of suitable patients from this group offers a wide latitude of choice. When pneumothorax treatment was first introduced it was limited to patients with unilateral disease. At present no such strict rule is followed. If the disease is relatively quiescent on one side and active on the other, pneumothorax may be safely induced on the active side. In most instances the other lung bears the added burden without apparent difficulty and often indeed gives evidence of improvement. When both lungs display active progressing disease, pneumothorax treatment is seldom beneficial and is not without danger. Unfortunately most advanced cases have bilateral active disease and for this reason pneumothorax treatment has a restricted field of usefulness. Hardly more than 5 per cent of advanced cases are suitable candidates for the treatment.

The only indication for inducing pneumothorax irrespective of the stage of the disease and the condition of the patient is profuse pulmonary hemorrhage. However, even this indication must be scrutinized with great care. Pulmonary bleeding is seldom profuse and in most instances stops before there is danger of fatal loss of blood. Fatal pulmonary hemorrhage is usually caused by the rupture of an aneurysm of the pulmonary artery and when this accident occurs there is not time to induce pneumothorax. However, patients sometimes have recurring moderate hemoptyses, bleeding once a day or twice a day for a week or longer. In these instances pneumothorax often has the happiest effect. When pneumothorax is induced to control bleeding the physician must decide whether he will maintain the pneumothorax for a long time or just long enough to control the bleeding. The decision is important because, when pneumothorax has been induced and the air has been absorbed and the layers of the pleura allowed to come together, they nearly always tightly adhere and make impossible any later pneumothorax treatment. When there is bilateral tuberculous involvement it is not always easy to tell from which lung the bleeding comes. It is not advisable to undertake pneumothorax treatment when this doubt exists. If desperate circumstances force the hand of the operator as much reliance may be put upon the sensations of the patient as upon the physical examination.

Effects of Induced Pneumothorax.—There is hardly any other therapeutic measure that produces such striking amelioration of symptoms as the induction of pneumothorax commonly does. Cough and sputum diminish, fever subsides, appetite returns and the patient's general condition quickly improves. The diminution of cough and sputum is especially noteworthy. Following the initial or the first few inflations, cough and sputum may be temporarily increased, but when sufficient air has been introduced to cause collapse they quickly diminish and often disappear. This effect of pneumothorax is easily understood. As the lung is compressed the purulent secretion in the bronchi and in cavities is squeezed out and cannot reaccumulate. The favorable influence of pneumothorax upon the general symptoms of intoxication is equally clear. The diseased lung is filled with the products of inflammatory reaction and the incessant expansion and retraction of the lung must facilitate absorption of these poisonous products. As the lung retracts these movements gradually subside and finally cease altogether. The lung is compressed to a small mass lying close to the spine which gradually undergoes fibrosis.

Aside from certain accidents, which are rare if a careful technic is followed, the induction of pneumothorax is remarkably well borne. Dyspnea is present only on exertion and even when the pneumothorax is complete patients are able to do a surprising amount of work without the least discomfort. Pain is sometimes complained of after inflations but it is seldom severe unless an effort is made to tear adhesions by raising the pressure.

This is not the place to discuss physical signs of pneumothorax. When the collapse is complete the classical signs are easily discovered. However, after the inflation of small amounts of air and particularly when adhesions prevent a uniform collapse, remarkably bizarre signs may appear. Without a knowledge of what had gone before it would be difficult to interpret them correctly. Some observers contend that it is unsafe to practice pneumothorax treatment without X-ray control. I do not share this overcautious view. If the patients are carefully studied by the usual technic of physical examination I believe that the method may be carried out successfully without additional risk.

Method of Inducing Pneumothorax.—The method devised by Forlanini, or some modification of this method, is now universally used. The apparatus consists of two bottles or cylinders connecting with one another at the base, a manometer, a three-way stopcock and a properly constructed needle. Air is forced from one bottle by the pressure of the water in the other and the pressure may be varied as desired by raising or lowering the bottle. The three-way stopcock is connected by rubber tubing with the bottle containing air, with the manometer and with the needle. When the lever points in one direction the bottle with air is connected with the manometer, in another direction the bottle with the needle and in the third direction the needle with the manometer. Such a simple apparatus I devised in 1910 and have continued to use since then with entire satisfaction. If a portable apparatus is desired, one devised by Robinson may be secured or the more elaborate one sold by The Kny-Scheerer Company. Formerly nitrogen was used for the pleural inflations under the supposition that nitrogen is more slowly absorbed from the pleural cavity than oxygen. However, gas analyses have thrown much doubt upon this supposition and what difference may exist between the absorption of nitrogen and of air is too small to be of practical importance in this connection. Air answers the purpose equally well and is therefore generally used.

The needle used for the operation deserves some attention. It should be of medium bore and sharpened obliquely with rounded point, something in the manner of a spinal puncture needle. The obturator should fit accurately to the end and a cock at the base of the needle connect it with the pressure apparatus. A very satisfactory needle has been devised by Floyd and Robinson.

In selecting the site for operation preference should be given to the lower axillary area. The muscles in this region are thin and the ribs may be easily separated. The patient lies upon the side with cushions beneath the chest so that the upper side is slightly bowed and the interspaces thus widened. A small amount of novocain is injected into the skin and the needle is thrust through the bleb thus formed and slowly along the tract to be followed by the pneumothorax needle. A puncture wound is made with a small sharp knife through the skin and subcutaneous tissue. The apparatus having been previously tested and sterilized the needle connected with the manometer is now carefully advanced into the interspace. Since the skin and subcutaneous tissues have been divided no resistance is encountered until the fascia of the intercostal muscle is reached. With a little added pressure the needle pierces this fascia, giving a characteristic sensation and often an audible pop. One is then sure that the point of the needle lies among the fibers of the intercostal muscle and another cautious advance forces it directly into the pleural space. The operator has the manometer before him, and if the pleura is not adherent, as soon as the point of the needle reaches the pleural space, the manometer records a marked negative pressure with wide respiratory variations. The extent of the variation depends upon the force of the respiratory efforts, usually equaling about minus 8 to minus 10 cm. water on inspiration, and minus 3 to minus 5 cm. in expiration.

When the pleural cavity is free from adhesions the operation invariably goes smoothly. When adhesions are present it is more complicated: (1) since the characteristic pleural variations in pressure are absent, and therefore one cannot tell with certainty when the needle is in the pleural space; and (2) collapse is rendered difficult and, if the adhesions be dense, impossible. Various measures have been suggested to overcome these obstacles.

For instance, Forlanini introduces the needle to a point where he thinks the pleural surface has been reached. He then very slowly and cautiously pushes the needle a little further in, and at each advance tests the position of the needle. For this purpose he compresses a small area of the rubber tubing between the fingers, thus forcing through the needle a very small amount of air under high pressure. If the needle is in the extrapleural tissue the manometer will show a negative pressure equal to the amount of air expelled from the tubing. Should the air vesicle be in close proximity to the pleura, respiratory variations may be recorded, but they are usually small in extent. If the point of the needle is between the two layers of the pleura and the expelled gas separates them, a more marked negative pressure is recorded than could be accounted for by the amount of nitrogen injected and the respiratory variations are wider. If the needle is in the lung, the manometer oscillates with respiration, but the mean pressure is about zero. If the needle is in the extrapleural tissue, or in a mass of dense pleural adhesions, the pressure rapidly rises, as gas is introduced in larger amounts, and gradually falls to normal as the gas diffuses throughout the tissue. Thus, in the instance of pleural adhesions, emphysema of the connective tissue is produced instead of pneumothorax.

In the presence of adhesions Saugman introduces the needle into the lung. The oscillations of the manometer indicate its position. The needle is then cautiously withdrawn until the oscillations cease. With a syringe that fits into the end of the needle, aspiration is performed. If no blood is obtained, he forces in air under a pressure of from 20 to 30 cm. water. If the pleuræ separate, a well-marked negative pressure may occur after a few cubic centimeters of air have been injected. Larger amounts of air may then be allowed to run in, although the operation is usually attended with great pain from the stretching and tearing of adhesions.

As I have stated, when the pleura is free, the operation of inducing pneumothorax is extremely simple. I have, in a few instances, when I was confident that the needle was in the pleural cavity, attempted to break up adhesions by injecting air under pressure. After from 50 to 100 c.c. of air have been injected, the patient complains of extreme pain and the manometer registers a high, positive pressure, often 15 to 20 cm. water. During the following few minutes the pressure gradually falls to rise again as more air is introduced. In this manner many hundred cubic centimeters may be injected, although the pleural surfaces remain adherent, and no pneumothorax is produced. I have, however, abandoned such ill-advised attempts. There is always danger of air embolism, and the infrequent success of efforts to separate forcibly an adherent pleura does not justify the risk assumed. When I am unable clearly to find a pleural space, instead of manipulating the needle, I prefer to withdraw it and try in another position. The procedure gives so little discomfort to the patient that one does not hesitate to make numerous punctures searching for a clear pleural space.

In this way all danger of air embolism is avoided. In one of my cases I made three fruitless efforts in the axillary region to hit the pleural cavity, but the fourth, made in the back below the angle of the scapula, was successful. A partial pneumothorax was produced which, after subsequent refillings, extended and became complete. In another instance eight attempts were made to induce pneumothorax, but to no avail. Another patient, in whom no pleural cavity could be demonstrated, was later operated upon by the Brauer method. The blunt cannula entered a dense network of pleural adhesions and it was impossible to produce a pneumothorax.

When adhesions are present and a small intrapleural air vesicle has been produced, Saugman advocates using high pressure to break up the adhesions. For months he has maintained a pressure of from 20 to 30 cm. water in the cavity. If the adhesions are dense, it is impossible to separate the pleuræ and the method frequently produces unpleasant results. Subcutaneous emphysema spreading over the thorax and abdomen is not uncommon. Less often, but more serious in its consequences, air enters the loose connective tissue between the costal pleura and the thoracic fascia and reaches the mediastinum. It may appear in the subcutaneous tissue of the neck and cause great pain, and, by pressure on the esophagus, difficulty in swallowing. Instances are reported in which the gas has pierced the diaphragm, probably in the connective tissues surrounding the aorta, and produced extensive subdiaphragmatic emphysema.

It is true that pleural adhesions frequently stretch and under continued gentle pressure allow the lung to collapse completely. If a fairly large air vesicle has been produced and the mediastinum is rigid, one may, with little discomfort to the patient, maintain an expiratory pressure of from 5 to 15 cm. of water, and note the gradual extension of the pneumothorax cavity and increasing collapse of the lung. There is always some, and often severe, pain where adhesions are attached.

If the adhesions are dense and, upon repeated punctures in different locations, no free pleural space can be found, it is wisest to abandon the attempt. Efforts forcibly to tear the adhesions under high pressure seldom succeed, and are attended by danger of air embolism and deep emphysema.

Pleural adhesions are then the main obstacle in the way of successfully inducing pneumothorax, and unfortunately their presence or absence cannot always be determined before the operation is undertaken. When the history of the illness points to frequent attacks of pleurisy, and particularly when physical signs indicate a thickened pleura, I am prepared for failure. When fluoroscopic examination and percussion on inspiration and expiration show a wide excursion of the lower lung border, I am equally confident that the operation will succeed. It is when the diaphragm movements are limited and there is no pleural dulness that definite predictions cannot be made. The diseased lung, as well as pleural adhesions, restricts movement, and, while a lack of proportion between the extent of disease and the amount of restriction may be a valuable indication, I cannot be certain of the result. If compression of the lung has been begun by a pleural exudate, one may maintain and increase the collapse by withdrawing the fluid and introducing gas. As the pleural surfaces are already separated there is no difficulty in finding the space. When the gas is introduced through the effusion, we are deprived of the information afforded by the manometer, as the pressure variations are not transmitted through the fluid.

The amount of air to introduce at the first inflation depends, in a meassure, upon the condition of the patient. If severe pain or dyspnea develop, only a few hundred cubic centimeters should be injected, otherwise it is advisable to give from 300 to 500 c.c. Forlanini and Saugman advocate giving from 100 to 200 c.c. and very gradually, by daily repetitions, to increase the amount. They feel that, in this way, the contents of the chest adjust themselves more satisfactorily to the changing conditions of pressure. However, I believe the importance of at once producing an appreciable collapse of the lung, so that subsequent inflations may be carried on without danger of piercing the organ, far outweighs this consideration. As a matter of experience, 500 c.c. of air may be introduced into the pleural cavity, even when the opposite lung is extensively diseased, without occasioning any unpleasant symptoms.

If the original inflation has been successful, the subsequent operations may be performed with great ease. A careful physical examination will usually indicate the position and extent of the pneumothorax, although X-ray examinations add wonderful precision to the observations. Stereoscopic plates, particularly, give an exact picture of the conditions and show the position of the lung and depth of the cavity at every point. For the second and subsequent injections a sharper needle of smaller bore may be used. If the lumen of the needle is free as soon as it enters the pleural space, the characteristic manometer oscillations occur and the gas should never be allowed to flow in if they are absent. When fine caliber needles are employed they frequently become plugged by a drop of blood or serum, or a bit of the subcutaneous fat. They may readily be cleaned by introducing the obturator in the manner previously described. If the needle is in the pleural cavity, the manometer will then at once show respiratory variations and the air is allowed to run in slowly under slight positive pressure. After each 100 c.c. the pleural pressures are read, and the amount introduced largely regulated by the pressure conditions.

In the beginning, inflations are made every second or third day. When the collapse is complete once a week suffices. Later, as the pleura loses its capacity for absorption, inflations at two and three-week intervals will maintain the collapse. At each inflation one estimates the amount of gas that has been absorbed by the amount necessary to bring the pleural pressure to the level of the end pressure of the previous inflation. Before collapse is complete, a few hundred cubic centimeters additional gas are added at each operation. Subsequently, if the pleural cavity is free, the pressure should be maintained that gives a slight positive elevation on inspiration. The normal pleural cavity absorbs from 80 to 100 c.c. nitrogen per day; after the pneumothorax has existed for some months it absorbs from 25 to 50 c.c. The pressure conditions vary somewhat in each individual case, and the amount of gas injected and the frequency of the inflations must depend absolutely upon the manometric record. When the pleural cavity is free it requires from four to five inflations before a positive pressure is reached. If adhesions are present, partly occluding the pleural cavity, a positive pressure may be recorded after the first inflation of from 500 to 800 c.c. Under these conditions a moderate positive pressure is maintained, and not infrequently the adhesions will subsequently yield.

The pneumothorax may be maintained for a year or more and the lung then allowed slowly to expand.

Throughout the whole procedure of inducing and maintaining pneumothorax, the manometer plays such an important part in guiding us that I shall review briefly the information it gives.

1. It indicates accurately when the needle has entered a free pleural space. The manometer at once records a negative pressure with marked respiratory variations.

2. When the needle is in the lung, respiratory oscillations occur, but they vary about the zero point. If the patient draws a deep breath and holds it, the manometer records a sudden negative pressure which quickly falls to normal. If the needle is in the pleural cavity, the negative pressure is maintained as long as the breath is held.

3. It indicates the size of the pleural space. If the pleura is free, many hundred cubic centimeters of gas must be introduced before the pressure is raised. If the pleura is partially obliterated or the pneumothorax cavity walled off, 500 or 600 c.c of gas may bring the pressure to zero. If the cavity be small, a few hundred cubic centimeters may occasino a marked positive pressure. In walled-off spaces the respiratory variations are smaller than in the free pleural cavity.

4. If the needle be extrapleural or be imbedded in pleural adhesions, no respiratory variations occur. If a small amount of gas be injected the manometer records a high positive pressure, which gradually falls to zero as the gas diffuses.

5. It indicates the absorbing power of the pleura, and accurately controls the frequency and amount of injections necessary to maintain the desired conditions.

6. It indicates the degree of elasticity of the compressed lung. Upon subsequent refillings, it there is a very gradual rise in pressure following the introduction of each 100 c.c. of gas, the lung has expanded with the

diminishing pleural pressure. If the lung has remained collapsed, there is little rise in pressure following the introduction of the first few portions of gas, and then a very sudden and marked rise upon the introduction of a further small portion.

7. Likewise a slow increase in pressure with wide respiratory variations indicates a flexible mediastinum; a rapid increase in pressure with small respiratory variations, a rigid mediastinum.

8. Von Muralt has observed a sudden fall in pressure during inflation, due to the giving way of pleural adhesions. In another instance the lung ruptured during an inflation and the pressure fell at once to zero, and showed no subsequent rise even when large amounts of gas were introduced.

9. Occasionally the manometer shows reverse respiratory oscillations, that is, a higher pressure with inspiration than with expiration, due to paradoxical movements of the diaphragm.

Complications of Induced Pneumothorax.—The complications occurring in induced pneumothorax are air embolism, infection, subcutaneous emphysema, pleural effusion and rupture of the lung.

The most serious and the most feared accident is air embolism. A few instances will illustrate its gravity. Lemke, in inducing pneumathorax, did not use a manometer, but determined that the needle was in the pleural cavity by instructing the patient to take deep breaths. An inrush of air occurring during inspiration indicated to him that the needle was in the proper position. At the second inflation upon a patient with extensive right-sided disease, the usual sound of inrushing air was missed. After two or three forced inspirations about three cubic inches (48 c.c.) of nitrogen had been sucked in when the patient complained of feeling weak, became pale and fell into a state of collapse. Respirations were stertorous, the pulse slow and weak. The needle was withdrawn and stimulants administered. As soon as the pulse improved, a careful examination was made and revealed complete right-sided hemiplegia. When the patient became conscious he had aphasia. Within twenty-four hours paralysis of the face had disappeared. Some months later the face was normal, the leg weak and spastic, and the arm had regained but little power. During a refilling, while nitrogen was flowing in through the needle, one of Brauer's patients suddenly moved. She complained at once of great pain, became unconscious and collapsed. After several hours there was evident hemiplegia, and six hours after the operation the patient died. A patient in whom pneumothorax had been successfully induced was allowed to wait too long for refilling, and the gas had been almost completely absorbed. At the second operation, although no characteristic manometric variations occurred, it was supposed that the opening of the needle was in the pleural cavity. Thinking the needle might be plugged, a little nitrogen was allowed to run in. The patient immediately collapsed, and in a few minutes was dead.

These unfortunate clinical results have not been reproduced experimentally. The lungs of healthy animals withstand, as Brauer himself asserts, a remarkable amount of trauma. He was unable to produce fatal air embolism in dogs, in spite of gross damage to the lung. However, operating with an aspirating needle, he found it impossible to reach the intrapleural space without producing some slight lesion of the visceral pleura. He believes that when the lung is diseased, even such trivial lesions may have serious consequences. Forlanini repeated these experiments. With great ease he could induce pneumothorax in dogs and, upon forcibly inflating the lungs after removal from the body, rupture always occurred first about the borders, and never at the position corresponding with the point of operation.

It is well known that large amounts of air may be injected into the systemic circulation without producing fatal air embolism. If large amounts are rapidly injected into the veins, death occurs from dilatation of the right ventricle and cardiac syncope. Ten to 12 c.c. of air per minute may be allowed to flow into a vein for an hour without producing any serious results. Fatal air embolism of the brain never follows the introduction of air into the systemic veins. Air introduced directly into the left ventricle or into the carotid artery immediately produces symptoms of cerebral embolism. Only very small amounts can be injected without danger. Forlanini finds that from 6 to 8 c.c. in the ventricle and from 2 to 3 c.c. in the carotids may be safely given.

Simple puncture of the lung with an aspirating needle, even when the organ is diseased, is associated with little danger. Daily exploratory punctures are made without hesitation in all large medical clinics. Serious air embolism has followed attempts to produce pneumothorax only upon the injection of gas in the absence of satisfactory evidence that the needle is in the pleural cavity.

I am fortunate enough never to have seen this accident. It is true that it has occurred under the treatment of experienced operators and not only at the first operation but at subsequent refillings. These accidents emphasize the extreme caution that should be used in performing the operation and the necessity for careful manometric control. If the manometer is carefully observed and its indications correctly interpreted, there is little danger of serious air embolism.

Some authors have spoken in detail of a group of symptoms they designate as pleural shock. The symptoms are not clearly distinguished from those of gas embolism and Brauer and others refuse to recognize a distinction. The symptoms vary in intensity from pallor, sweating, dyspnea and tachycardia that pass in a few minutes or an hour to alarming prostration that may end in death. The distinction from air embolism is based upon the fact that (1) this group of symptoms may recur in the same patient at three or four consecutive refillings; and (2) that they may follow pleural trauma without gas inflations, for instance the injection of novocain. The dispute is not yet settled but general considerations lead me to distrust the view that pleural shock can cause death.

Infection of the pleural cavity may occur from without or through the lung. It is needless to emphasize the ease with which the pleural cavity may be infected and superfluous to insist upon the importance of a rigid surgical technic in all the manipulations. Even with great care infection of the wound will occasionally occur and spread to the pleura. A more common cause of infection is pulmonary rupture. This occurs often enough to be a matter for serious consideration. No doubt rupture is often facilitated by the tug of firm adhesions. Whether infection comes from within or without a pyopneumothorax rapidly results and is often quickly fatal. Even when the patient does not succumb a difficult situation results, the proper management of which taxes medical and surgical ingenuity. Permanent drainage must usually be established and in the end the patient faces the alternative of such continued drainage or an extensive plastic operation to obliterate the cavity by collapse of the chest wall. Neither of the two is an inviting prospect.

It is common for a little air to escape about the puncture wound into the subcutaneous tissue. This causes a more or less marked crepitating swelling. It is of no practical significance. At times air separates the parietal pleura from the chest wall and at a susequent inflation the needle may enter this bleb and, since the manometer records oscillations, air may be introduced under the misapprehension that the needle is in the pleural cavity. The air quickly forces its way through the mediastinum to the subcutaneous tissue of the neck and is recognized by the characteristic crepitation. When air escapes into the deep extrapleural tissues it may travel in any direction. Usually it goes to the neck and arms or chest wall but it may wander to the abdominal wall and even to the scrotum and thighs. Instances are reported in which the air has pierced the diaphragm, probably in the connective tissue about the aorta, and produced extensive subdiaphragmatic emphysema. Subcutaneous emphysema is an unpleasant but otherwise harmless complication. Pain is the common symptom and, when the air has infiltrated the mediastinum, dysphagia and dyspnea are often complained of. The complication seldom occurs to any marked degree except when in the presence of adhesions air is forced into the pleural cavity under high pressure. The tympanitic note given by the air upon percussion may lead to the false impression that a large pneumothorax has been produced.

Pleural effusion is the most frequent complication of induced pneumothorax. After the pneumothorax has been maintained for some time a small amount of effusion almost regularly occurs. These small effusions give no symptoms and in no way interfere with the treatment. They may be disregarded. In 20 to 30 per cent of the cases more massive effusions occur. Sometimes they come on with stormy symptoms, pain, high fever and prostration. Some authors advise that the fluid be withdrawn and replaced with air, but in my experience it usually works better to leave them unmolested unless urgent dyspnea makes it necessary to remove them. If the effusion occurs when the lung is completely collapsed they may persist for years. If the lung is only partially collapsed it is seldom possible to produce full collapse thereafter. A rapid resorption of the fluid may allow the lung to expand quickly and if the pleural surfaces once become opposed they adhere and further treatment is impossible. Sometimes the effusion becomes infected without there being a definite pulmonary rupture. The patient then develops a pyopneumothorax with the attending serious symptoms.

In apparently healthy individuals the lung sometimes ruptures, causing a spontaneous pneumothorax. In these instances the symptoms are often trivial, no infection of the pleural cavity occurs, and the air is quickly absorbed. The pleural rent must be very small and as the lung collapses the opening closes and quickly heals. A similar accident sometimes occurs during pneumothorax treatment. Only a small amount of air may be introduced and yet at examination a considerable collapse may be discovered. One author reports the occurrence of this accident as he was preparing to induce pneumothorax. The accident is due to the rupture of an emphysematous bleb or to a small tear in the pleura from the tug of adhesions. These innocent accidents are not followed by any important consequences. They are distinguished from larger pulmonary ruptures by the absence of infection of the pleural cavity. When larger ruptures occur infection always follows accompanied by the stormy symptoms of pyopneumothorax.

HELIOTHERAPY IN TUBERCULOSIS

JOHN H. PRYOR

Since the beginning of the history of the human race the life-giving powers of the sun have been recognized. The Egyptians and the Persians, perceiving but not comprehending these powers, embodied them in their religious beliefs. It remained for the Greeks and the Romans to bring sunlight definitely into the realm of therapeutics. On the advice of their physicians, they built solaria in their homes and on their terraces in which they exposed their nude bodies to the sun's action. Herodotus mentions sunlight in his writings; and Hippocrates, the founder of climatology and climatotherapy, was the first to employ its energy in the treatment of tuberculosis of the lungs.

During the centuries that followed (the Dark Ages), heliotherapy seems to have fallen into disuse, until in 1800 it was revived by the French. Since then the physiological and therapeutic effects of light from both natural and artificial sources have been made the subject of more or less careful study, stimulated by the fact that in spite of its wide use and acknowledged virtue the real nature of its action has remained a mystery.

Various theories regarding its action have been suggested. Those who have believed that the beneficial value of light is confined to a certain portion of the spectrum have tried to substantiate their theories by the use of lights rich in that particular ray, hoping also in this way to overcome the difficulty presented by the fact that the sun's radiant energy is not always available.

Clinicians who contributed early to our knowledge of the sun's therapeutic application were Bertrand and Leconte. About 1840 Bonnet, Poncet and Ollier employed sunlight in the treatment of joint diseases in general and reported encouraging results. In 1899 Finsen published his work on the effects of the short wave-length rays, violet and ultraviolet, upon lupus, and the value of the red rays in smallpox. Bernard in 1902 noticed the action of light upon suppurating wounds. Rollier at Leysin in 1903 began his treatment of tuberculosis by means of heliotherapy. He was the first to apply the sun's energy in a systematic manner and his original technic has been universally followed by successful heliotherapists. Malgat in 1904 treated pulmonary tuberculosis by sunlight. Kime in 1903 used light in the treatment of lupus and in 1904 both he and Malgat applied it in pulmonary tuberculosis. Lenkei began its use in 1908. In this country the author, with the coöperation of Hyde and Lo Grasso instituted heliotherapy as a predominant part of their treatment of tuberculosis in 1913. Just as Rollier was the first to standardize and scientifically utilize sunlight in the treatment of tuberculosis in Europe, the J. N. Adam Memorial Hospital was the pioneer institution to apply sun cure extensively in America. From this brief history of light therapeusis we learn that sunlight as a curative factor is as old as the practice of medicine; and, although much has been accomplished in the past, it is to the future that we must look for a more specific knowledge of its action and a more scientific application of this therapeutic agent in health and disease.

As one reviews the literature on the action of light, whether sunlight as a whole or any one of its individual rays, one immediately notes the many and great discrepancies that have occurred in the work of the different experimenters. These differences of opinion are primarily due to the fact that, up to the present, fundamental and rudimentary facts of light action are lacking. Experiments conducted by the various investigators have been done under varying conditions with the result that opposing conclusions have been drawn. At the present time two schools exist, the one giving to certain portions of the sun's spectrum greater action than other parts or whole sunlight; the other holding to the theory that all parts of the solar spectrum are of value, and that with our present limited knowledge we cannot attribute beneficial powers to any one portion of the sun's energy to the exclusion of the others. The author, LoGrasso and Balderrey subscribe to the latter view. Rollier says:

> "Although it cannot be denied that excellent therapeutic results have been obtained with artificial light, especially with ultraviolet rays produced by the mercury vapor lamp, I am strongly of the opinion that, up to the present, science has not yet invented an adequate substitute for sunlight; on this point I have the support of Finsen himself, who admitted that the ideal treatment of lupus was heliotherapy at a high altitude."

Effects of Light on Bacteria.—Sunlight is very destructive to bacteria. The time required for this action depends upon the intensity and quality of the light, temperature, condition of bacteria, moist or dry, age of culture and type and biologic properties of the organism. The action of light upon bacteria is supposed to rest chiefly with the blue, indigo, violet, infra-red and ultraviolet rays. The greatest bactericidal action is given to the ultraviolet portion of the spectrum. It has been demonstrated that bacteria upon media are killed by this part of the spectrum; but, if the bacteria are covered by very thin layers of the media, they are not affected. In the skin, bacteria may be killed at a depth of 1.5 mm. and their virulence diminished at a depth of 4 mm. It has also been shown that ultraviolet rays of sufficient strength to kill bacteria at a depth of 0.2 mm. are also strong enough to destroy epithelial cells at a depth of 0.5 mm. in one hour. Weisner has shown that the infra-reds are as powerfully bactericidal as the ultraviolets. Bie, working with the Bacillus prodigiosus, found that all the frequencies of the visible spectrum and the ultraviolets of the invisible (infra-reds not studied) in ratio increasing from red onward, checked bacterial development, the greatest action being noted from the blue to the ultraviolet. Trekenskaja, in comparing the action on bacteria of sunlight at different altitudes, found that the results obtained were the same at an elevation of 1,560 meters (Davos) as at sea level (St. Petersburg). Von Bergen disagrees with this report, finding that at the different seasons of the year at an elevation of 1,360 meters varying periods of exposure were necessary to destroy bacteria. Concentrated sunlight was found by Finsen to kill bacteria fifteen times more rapidly than ordinary sunlight. Only when the various investigators observe uniform methods, measuring the intensity of the solar energy or artificial source of light, making accurate observations as to temperature and wave-lengths present or used and taking into account such factors as the possible interfering influence of the reactions of the culture media upon bacterial growth, will similarity in results be found. At present we are safe in saying that light is bactericidal; but in the laboratory much remains to be done and a standardization of the technic must be made and followed. As to the bactericidal action of light in the deeper tissues, one might venture the opinion that the growth of organisms is inhibited by the action of the deeply penetrant infra-reds, basing this upon the increased inflammatory reaction causing increased exudation of serum, and the migration of leukocytes promoting phagocytosis. Verhoeff and Bell in speaking of the destruction of bacteria within the cornea or any other tissue of the body say:

> "Abiotic radiations possess no therapeutic value. This is due to the fact that abiotic radiations that are able to penetrate the tissues are more destructive to the latter than to the bacteria."

Jansen held the view that sunlight acted as a caustic and not as a germicide.

Effect of Light on the Skin.—The physiological changes occurring in the body caused by light are as yet not fully known. Some few studies are fairly complete. The changes noted in the histology of the normal skin after exposure to sunlight have been studied and it has been found that macroscopically the skin presented an acute erythema. Microscopically, there is a dilatation of the superficial and deep blood-vessels; increased exudation of serum, particularly in the corium; slight elevation of the horny layer and separation from the granular stratum; migration of leukocytes with slight infiltration; dilation of the lymph spaces and in the basal layer more karyokinesis than normal. With radiation of normal skin there are three types of reaction: heat erythema, appearing after from eight to ten minutes; light erythema, resembling a burn of the first degree, with a short latent period of from three to six hours following radiation; and pigmentation occurring in from four to six days.

The following theories have been advanced as to the function of pigment:

1. That it is a natural protective measure against the irritating effects of the ultraviolet rays, thus permitting the exposure of the body to the action of sunlight for longer periods of time.
2. That it has the power to transform the short wave-length ultraviolet rays to longer and more penetrating ones.
3. That it changes the absorbed rays to living energy.

Careful observations of the coloring of animals have revealed facts which seem to substantiate the above-mentioned theory that pigmentation is a protective agent against the caustic action of the ultraviolet light. The lower vertebrates exposed to the sun have pigmented mesoderms in those instances where the ectoderm is devoid of pigment, and this protective pigment is only present on the surface which is exposed to the sun's rays. Tropical animals as a rule have black skins; the exceptions to this have red or yellow pigment or are so thickly covered by hair or feathers as to need no further protection. In the white race the pia mater of the cervical cord, which is most exposed to light, contains pigment which in the other portions of the cord is absent. Woodruff says:

> "As a rule, in races of men, the amount of pigment is sufficient to protect from the maximum amount of ultraviolet light to which he is exposed at any time in the year in the climate which evolved the type."

Without this means of adaptation to the solar environment, the development and progress of the human race would be greatly impeded. That pigmentation may have other functions in addition to that of protection must be admitted, but a greater or more important one would be inconceivable.

A theory perhaps equally as important as those previously advanced is suggested by the author and his coworkers LoGrasso and Balderrey. It is believed that tanning of the skin changes the white reflecting, less absorbing surface of the body, to one which permits greater penetration and absorption of light, particularly the long wave-length rays. If it is true then that "only the rays absorbed are effective in producing chemical change" (Gratthus) by increased pigmentation and absorption greater dosages of light are available. The law of radiation is the reverse of that of absorption so that, although tanning increases heat absorption and production, there is also an increased ability of the body to radiate heat which prevents heat insolation or sunstroke and permits us to give extended periods of solar radiation with its accompanying hyperemia.

4. The theory as to the transformation of wave-lengths by pigment has been held by Rollier and Mierowsky, but has never been demonstrated, as a solvent has not been found for melanin.

Effect of Light on the Circulatory System.—The effects of light upon the circulatory system have been very carefully studied. The blood-vessels are affected first, a dilation of the cutaneous vessels taking place. There is a lowering of blood-pressure. Ultraviolet radiation does not influence the pulse rate, but with solar radiations an increase may be noted. An increase in hemoglobin and the number of red blood-cells is found and this has been attributed to the altitude rather than to light. If a leukocytosis exists, an increase in the polymorphonuclear cells is present in the beginning, but later examinations show a decrease in the number of white cells with an increase in the lymphocytes. Under the influence of light, hemoglobin gives off its oxygen more quickly than in the dark. This would indicate that the oxidizing power of the blood is increased and thereby the process of oxidation in the body is encouraged. Ultraviolet rays have no effect upon the erythrocytes. They decrease blood-pressure, diminish the number of leukocytes and cause a lymphocytosis.

A stimulating effect is found upon the vasomotor system. This is probably due to the infra-red, red and ultraviolet rays. Respirations are slower and deeper after exposure to sunlight. These conditions are at times found upon radiation with ultraviolet rays. It is noticed that more rapid oxidation of tissue takes place with an increase in elimination of CO_2 and increased excretion of urine, urea and chlorids. All assimilative processes are stimulated and there is a rise in the calcium and phosphorus content of the blood with stabilization of the calcium in the bony structure. The cutaneous nerves are especially susceptible to the so-called chemical (blue to ultraviolet) rays. By the influence of these rays strong excitant or tonic impressions are constantly made upon the central nervous system, thus maintaining an efficient activity in every vital organ. Patients may become irritable or nervous under solar or ultraviolet radiations, but as a rule a quieting effect is noted. This soothing influence is particularly pronounced in the blue portion of the spectrum.

The body temperature varies greatly. As a rule, however, where fever exists, a gradual consistent lowering of the temperature occurs.

Elimination is favored through the lungs, kidneys and skin. Diuresis may be present following ultraviolet radiations, and albumin may be found in the urine.

Theories of the Action of Light.—Many theories are advanced as to the action of light, but they have not been substantiated as yet. The following are briefly presented:

1. Pigment is carried to the deep viscera by the blood-stream and focal reactions are set up.
2. Metabolic changes are caused by light and the pigment converts the short wave-length rays to long wave-length rays that are more penetrating.
3. Stimulation of the skin by light causes it to send out large numbers of antibodies.
4. The action of light upon the nerves of the skin and blood-vessels causes vasomotor stimulation, increases oxygenation and has a direct effect upon the tissue ferments.

5. Radiant energy, the exact nature of which is unexplained, is absorbed by the capillaries of the skin and carried to the depths.
6. Light breaks down the skin proteins and these act as antigens.

It may be true of the human body, as it is of plant life, that different cells respond to different rays. If this theory were proved, the beneficial effects of sunlight might easily be explained. It would also be quite clear why natural sunlight with its complete range of rays has given more satisfactory results than less complete artificial lights.

Pathological Effects of Light.—Pathologically sunlight produces a hyperemia. It changes a passive congestion to an active one. There is dilatation of the blood-vessels, migration of leukocytes, extravasation of serum into the tissues and increased connective tissue formation. Severe erythema with burning and blistering of the skin will take place if the skin is unaccustomed to the sun's action. Heat insolation and heat stroke are conditions noted when exposure to the sun's energy has been made in those unaccustomed to its action or when the radiation has been over too long a period of time. Ultraviolet rays are caustic in their action, rapidly producing an erythema and burn. Their effect upon the eyes is also caustic, blindness resulting if the action is too prolonged. The infra-red and red rays are most instrumental in causing heat insolation and stroke. Their action is particularly inflammatory. In the presence of humidity they increase the production of carbonic acid; affect the cortex of the brain, causing epileptiform or tetanic seizures; and may influence metabolism. Green rays do not cause inflammatory changes but exposure to these rays is depressing; physical processes are retarded. From the blue to the violet inflammatory reactions are found.

The secret of the sun's action on pathological processes is that, while it is highly toxic to bacteria in general and the tubercle bacillus in particular, the solar radiations are beneficial to the cells of the individual. It appears to increase the rate of disintegration of cells damaged beyond repair while stimulating the activity of those which are undamaged.

Penetrative Effects of Light.—That sunlight will penetrate the human body has been proved by Malgat, Finsen, Kime, Lenkei, Schamberg and others. As to the penetration of the individual rays, Finsen states "that the penetrating power of the different colors is inversely proportionate to their power of producing inflammation." He found that the short length ultraviolet rays were absorbed by the epidermis and that the inner long length rays as well as the blue violet reached the capillary network of the blood. Schmidt found that the penetration of the red rays through fatty tissues took place in one second and through muscle in one minute. Lenkei by the use of blue and yellow rays was able to penetrate tissues a distance of one inch, but in the absence of muscle this was increased to three inches. The red rays he found to be still more penetrant. Kaiser, by excluding all of the rays except the blue and violet, obtained impressions upon photographic plates through the chest. Busk was unable to obtain this result through his hand in ten minutes. Finsen, Malgat, Kime and Kaiser have obtained impressions of objects on photographic plates by passing sunlight through the chest. These results have also been obtained at the J. N. Adam Memorial Hospital. It is most unfortunate that in this work the intensity of the light was not measured and a spectrum analysis was not made, but these two factors will be dealt with in future experiments. The temperature, character of sky (clear, cloudy), humidity, time of experiment, direction of wind and barometric pressure were all included in the observations. Eastman Panchromatic Plates were used. The various types of light tested were sunlight; red rays (wave-lengths 580 to 700, total light transmission 22 per cent); green rays (wave-lengths 480 to 610, total light transmission 23 per cent) and blue rays (wave-lengths 480 to 510, total light transmission 1 per cent). By combining other filters it was possible to exclude all but one single portion of the visible spectrum, but in so doing the total transmission was at times so small that impressions upon the plates were obtained only through thin portions of tissue under the most favorable light conditions. Ultraviolet rays were obtained from a Hanovia lamp. Concentration of light was accomplished by using the Thezac-Porsmeur Lens.

From these experiments one might conclude that sunlight will penetrate the body to a depth of ten inches; that the penetrative power of the individual ray increases as refrangibility decreases; that concentration of light favors penetration and that pigmentation is an important factor in promoting light penetration.

Climate

Heliotherapy may be practiced in any place where the sun shines; but different localities show great variations in the quality and quantity of the sun's light.

In reaching sea level the sun's rays must pass through the whole thickness of the atmosphere. In and near large cities the air is heavily laden with mist, dust, smoke and microörganisms which absorb heat and light rays. This loss of energy by absorption diminishes the efficiency of the sun's energy. The increased humidity also overheats the air to such an extent that the sun bath may have a relaxing, even a depressing, effect, rather than the desired stimulating one. In higher altitudes the atmosphere is free from solid particles, humidity is less and the maximum quantity of light is available without loss by absorption. For these reasons greater intensities of sunlight can be borne at higher altitudes, but it must not be taken for granted that these localities are free from rain and cloudy days for they also have months when solar radiation is almost impossible.

To obtain the best results from heliotherapy it is necessary that a definite technic be followed. The individual's adaptability to this form of treatment requires careful observations so that excessive or harmful reactions may be avoided.

Upon admission of the patient to the hospital, casts (if in use) should be removed and the individual gradually accustomed to life in the open. The procedure followed is first to have the patient rest and sleep inside with doors and windows open. After becoming inured to the air he should be placed in the shade on an open porch for an hour or two, the time being gradually increased until practically all of the twenty-four hours are spent outdoors. This stage of the treatment may occupy a period of from seven to ten days, depending upon the physical condition of the patient, the season of the year and the character of the weather. Robust patients used to outdoor conditions may, during the summer months, be subjected to exposure to the sun immediately upon admission; but the hectic, emaciated and bedridden type must be very gradually adapted to the out-of-door life.

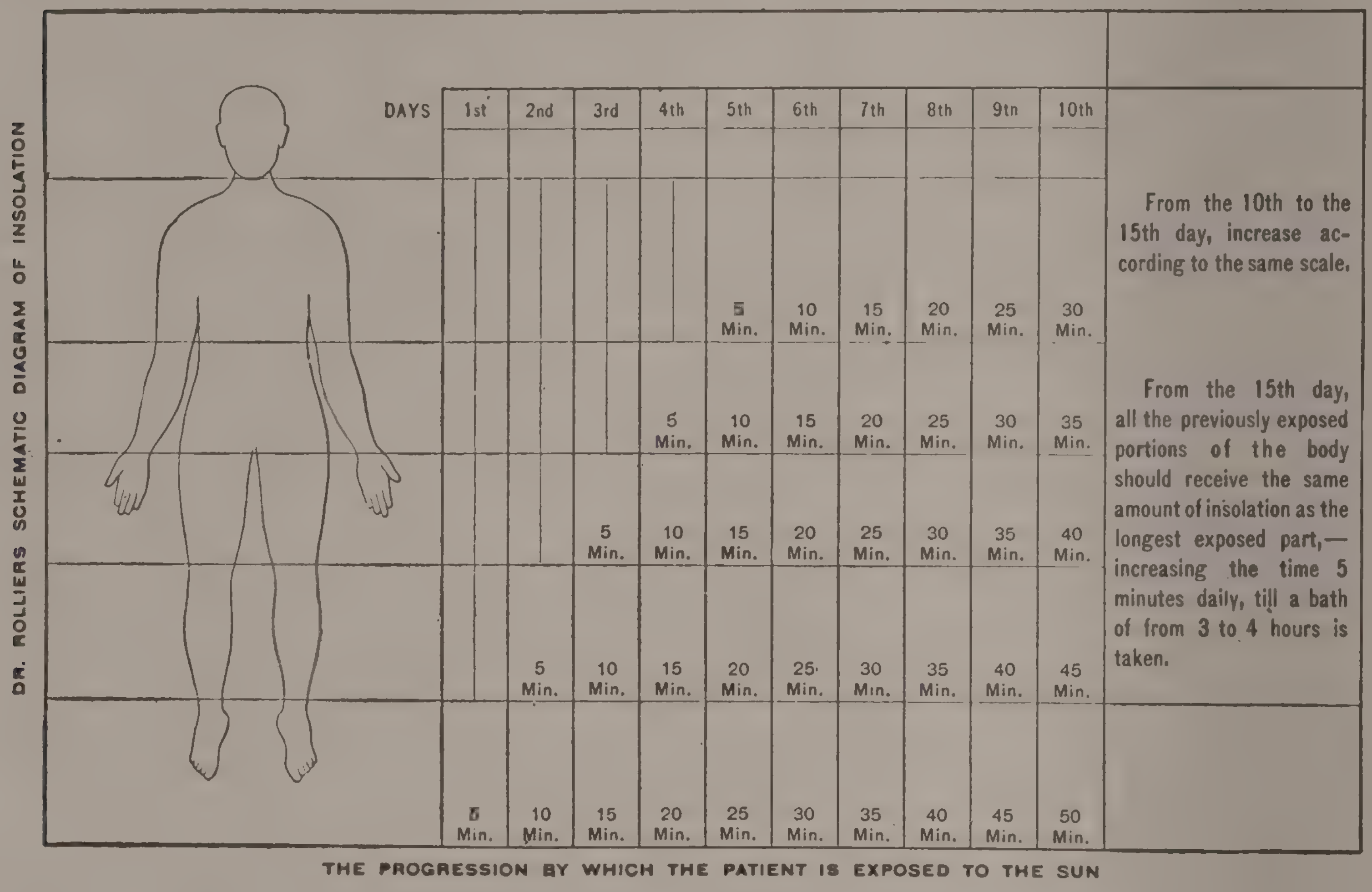
During this time careful observations should be made of the patient, and records of the temperature, pulse, respirations and the urinary and blood findings noted.

Following this preparatory stage the patient is ready for solar radiation.

Sun cure should not be given later than one-half hour before a meal and not earlier than one hour or preferably two hours after. During the hot summer months radiations must not be given during the middle of the day as at this period the intensity of the solar energy is at its maximum and a more or less severe reaction (heat insolation) with headache, rise of temperature, nausea, vomiting, rapid pulse and other constitutional disturbances may occur. The exposures are made with the patient in the recumbent position. The head must always be protected either by cap, umbrella or awning. The eyes are shielded by means of colored glasses or a towel placed over the eyes and forehead. Care must be exercised that a breeze does not strike the body.

In choosing the site for the construction of a building for sun cure consideration must be given to wind protection. It should be so situated that adequate shelter from the prevailing winds of the locality is afforded. Additional security may be furnished by wind-breaks or screens since a slight breeze striking the body may chill the patient and render him susceptible to colds. In those patients with high fever (102° F.), markedly poor physical condition and greatly lowered resistance, exposures to the sun must be more gradual. Too careful observation of these cases cannot be exercised and exposures should be shortened or entirely discontinued for a few days if any ill effects arise. In the event that radiations are interrupted for a short time, the first exposure upon resumption of the treatment should be for a shorter period of time than that of the last radiation when the exposures were discontinued. Severe irritation of the skin must be avoided not only because of its effect upon the patient but for the chief reason that these erythematous areas are difficult to tan.

Patients should be cautioned and prevented from overexposing themselves to light so that local and general reactions are prevented. Open lesions are not to be exposed until after the whole body has been uncovered to the sun's rays. Sinuses or ulcers may be covered with a wire screen as a protection against flies, and in children it also prevents injury to the lesion. These lesions may be cleaned with alcohol and dressed with gauze moistened with it.



DAYS	1st	2nd	3rd	4th	5th	6th	7th	8th	9tn	10th
					5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.
				5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.	35 Min.
			5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.	35 Min.	40 Min.
		5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.	35 Min.	40 Min.	45 Min.
	5 Min.	10 Min.	15 Min.	20 Min.	25 Min.	30 Min.	35 Min.	40 Min.	45 Min.	50 Min.

From the 10th to the 15th day, increase according to the same scale.

From the 15th day, all the previously exposed portions of the body should receive the same amount of insolation as the longest exposed part,—increasing the time 5 minutes daily, till a bath of from 3 to 4 hours is taken.

THE PROGRESSION BY WHICH THE PATIENT IS EXPOSED TO THE SUN

FIG. 1.—DR. ROLLIER'S SCHEMATIC DIAGRAM OF INSOLATION.

After each radiation the patient may be vigorously rubbed with spirits of camphor as an aid in hardening the skin. In extremely rare instances the skin may be so sensitive as to require the application of vegetable oil, such as coconut or olive oil, before exposure to the sun.

The following method, which is practically the one used by Dr. Rollier, is carried out at the J. N. Adam Memorial Hospital:

First Day.—The feet are exposed and bathed in the sun's rays for five minutes, three or four times at hour intervals.

Second Day.—The feet are insolated ten minutes and the legs from ankles to knees five minutes, three or four times at hour intervals.

Third Day.—The feet are insolated fifteen minutes, the legs from ankles to knees ten minutes, and the thighs five minutes, three or four times at hour intervals.

Fourth Day.—The insolation of the previously exposed parts is increased by five minutes, and the abdomen is exposed five minutes, three or four times at hour intervals.

Fifth Day.—Again the insolation of the previously exposed parts is increased by five minutes, and the chest is exposed five minutes, three or four times at hour intervals.

Sixth Day.—If the condition allows it, the patient is turned on his abdomen and the same course as described above is repeated.

Provided that the patient's condition allows it, instead of waiting for the sixth day to turn him on his abdomen in order to radiate the back of the body, from the first day, radiation of the front and back of every exposed part alternately may be practiced three or four times a day at hour intervals.

The solar radiation is increased five or ten minutes each time until three or four hours daily are taken.

The following simpler method in which the whole body is exposed from the very first day has been tried and found more satisfactory:

The first day the patient, using the same eye and head protection as with the above method, is radiated for two minutes three times in the morning and three times in the afternoon at hour intervals. Each of the six exposure periods is increased two minutes daily for fifteen days, when the total daily period of radiation will have reached three hours.

The number of exposures may then be reduced to two in the morning and two in the afternoon at hour intervals.

Strong and robust patients may take four hours of sun a day but three hours is sufficient for the majority of patients.

As the action of the air upon the skin is of great importance, in the last year it has been insisted upon that the patients, after taking the sun treatment, should be naked, except for the loin cloth, as much of the rest of the day as possible, so that the skin can be exposed to the stimulating effect of the air. Throughout the summer months children need rarely dress but may go to their meals and roam about in their trunks. Since this addition has been made to the sun cure treatment, the results noted have been a great deal better.

During the winter months, regardless of sun conditions, patients may be given air baths. The length of time for these exposures depends upon the degree of pigmentation and the physical condition of the patient.

Children who are permitted to exercise may be allowed to play in the open on calm, sunny days for periods up to one hour even when the temperature is as low as from 6° to 2° above zero.

At this point it is well to emphasize again the importance of wind protection when giving air baths during cold weather. It is absolutely necessary that no breeze strike the body. Even when exercising, well-protected places must be selected, unless the days are extremely calm.

In the course of the sun treatment the skin gradually takes on a bronze hue, then a copper color, and finally a beautiful chocolate brown. As pigmentation progresses the skin becomes supple and velvety and free from blemishes.

The favorable progress of the cure is in direct proportion to the intensity of the pigmentation. Patients do not seem to show much improvement until tanning takes place.

Persons of the brunette type tan the best while the freckle and red-haired are the poorest subjects. The latter burn easily but with perseverance they finally tan. It sometimes takes a year for this type to show pigmentation. What surprises one most is the perfect physical development and firm musculature of patients who have been in bed even for years.

The effect of solar radiation on the general condition of the patient is very gratifying to patient and physician alike. The haggard and spiritless appearance gives way to one of cheerfulness and animation. There is a rapid alleviation of pain and usually within two weeks complete disappearance; temperature gradually comes down to normal; appetite returns; weight and strength are taken on rapidly and the blood condition improves. Both hemoglobin and red cells increase, leukocytosis, if present, becomes reduced and an actual lymphocytosis takes place.

The outstanding local result in the not too advanced cases of joint tuberculosis is the gradual restoration of motion, partial or complete, in the affected joint. Whereas in the ordinary expectant treatment with casts or by operative procedure the prognosis depends upon the completeness of the ankylosis, in heliotherapy the aim is to restore the full function of the joint.

The action of the sun upon tissue is one of repair. There is an intense recalcification and a spontaneous expulsion of sequestra. The effect upon lymph-nodes is one of gradual shrinkage and in broken-down glands very often one of absorption or calcification.

The effect on effusions is one of absorption. This is best noticed in peritonitis and pleurisy.

Abscesses are usually absorbed but they frequently become calcified. Oftentimes they have to be repeatedly aspirated.

Sinuses at first react, as shown by profuse discharge and sloughing, but this is followed by the formation of healthy granulations and the gradual drying up and healing of the sinus.

The discarding of all casts in heliotherapy has led many to believe that immobilization is dispensed with in sun cure. On the contrary, immobilization is one of the requisites in solar radiation. It cannot be emphasized too strongly that the Rollier method of heliotherapy is not mere exposure to sun, but a combination of the sun treatment along with a specially devised method of fixation by rest in bed, by traction and by positions arranged with hard pillows—a combination which increases the resisting power of the patient, preserves or restores the natural function of the joint and prevents or corrects deformity.

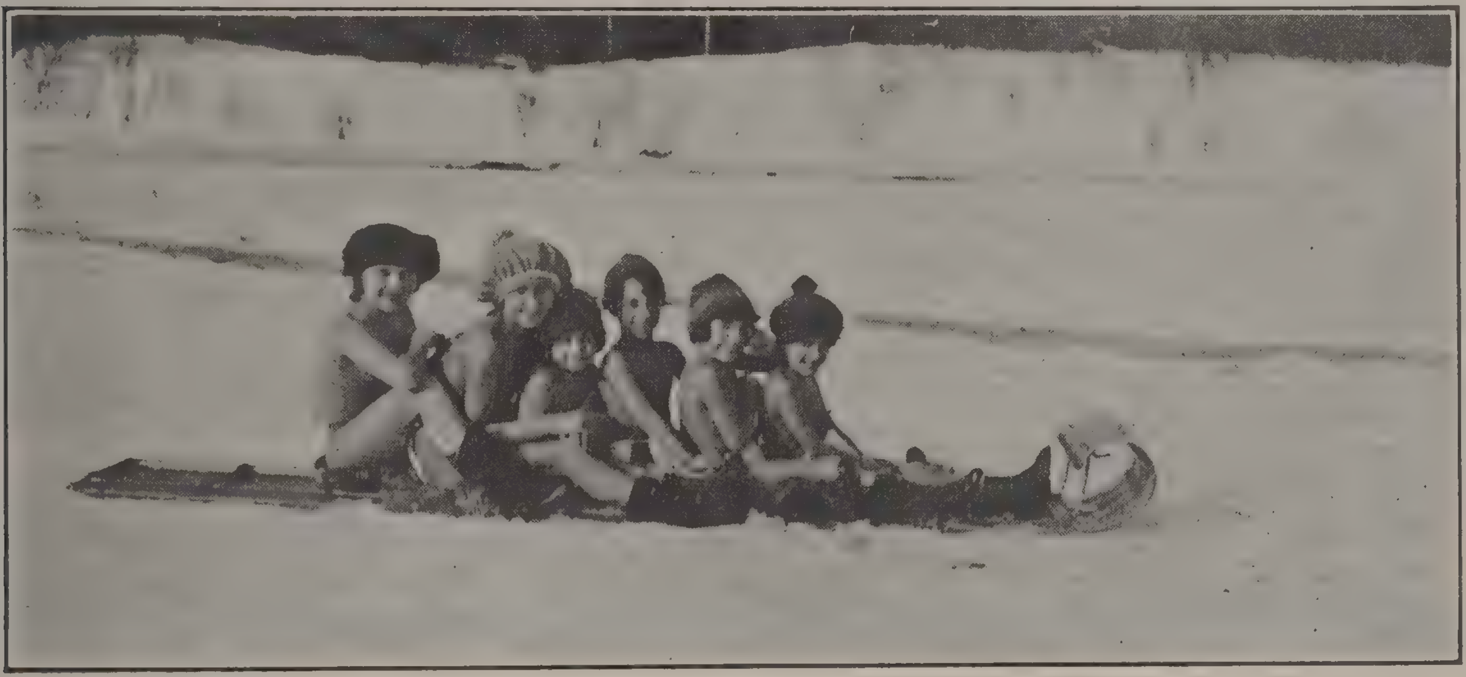


Fig. 2.—Showing Habituation to Exposure.

The type of case usually treated by heliotherapy has in the past been termed surgical tuberculosis. This is a misnomer and its use should be discontinued. In former years, it is true, these cases usually came under the observation and care of the surgeon; but with our present knowledge that operations are contra-indicated in the great majority of these cases, that a high percentage of them also have pulmonary lesions and that heliotherapy can be used with equally good results in all cases regardless of the organ or structure involved, it would seem best not to use the treatment prescribed as a basis for classification of the various manifestations of the disease as surgical or medical. Recognizing that the local manifestations represent only the further invasion of the body by the disease, we must bear in mind the fact that although special therapeutic measures may be indicated we are still dealing with tuberculosis, a general disease in which resistance plays a major rôle, and in which the efforts of the physician must be concentrated on improving the patient's general condition.

SPECIAL ORTHOPEDIC THERAPEUTIC MEASURES

Tuberculosis of the Spine.—Plaster jackets and similar fixation appliances should not be used when heliotherapy is employed as a therapeutic agent in the treatment of Pott's disease. The apparatus used for the immobilization, which is essential, should be so modified that the whole body can be easily exposed to the sun's rays. A hard pillow may be placed under the kyphos, and, when the patient is turned on the stomach, a triangular pillow with the base up is inserted under the chest, thus producing a compensating lordosis in both positions. In this way the deformity, unless very severe and ankylosed, is gradually reduced. In cervical cases the Bradford or Whitman frame with traction from the chin and occiput and countertraction by straps over the shoulders, elevation of the head of the bed and sandbags at each side of the head usually prove effective. In dorsal and lumbar lesions the hard pillows employed by Rollier give satisfactory results in most cases. The initial deformity should be accepted and diminution of the kyphotic prominence should be accomplished by creating compensatory curves in the normal spine above and below the lesion, according to the principles set forth by Calve. Spontaneous rupture of abscesses should be prevented by aspiration whenever possible. The needle should pass diagonally through healthy tissue which may act as a valve to close the puncture. A pad held over the abscess by means of a firm pressure bandage is indicated to prevent bleeding. Where pus is thick, aspiration may be done after injection of 5 c.c. of the following emulsion: creosote 2 parts; iodoform 5 parts; guaiacol 2 parts; ether 10 parts; sterile olive oil 100 parts. This helps to liquefy pus. Monthly examination, with anterior-posterior and lateral X-ray views of the affected spine every three months, are essential in order to determine the progress of the case.

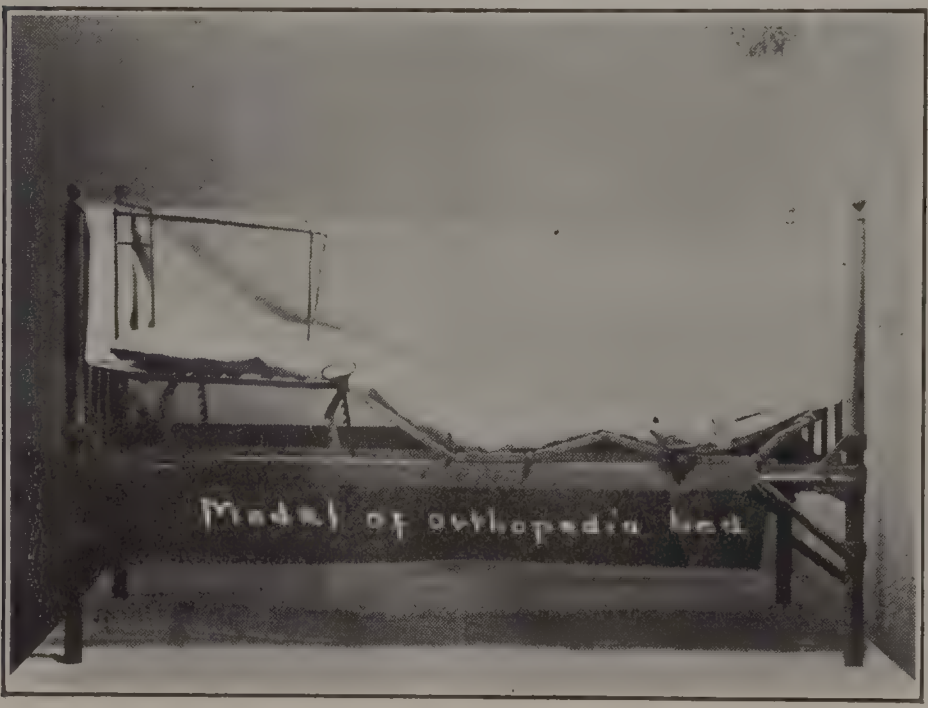


FIG. 3.—MODEL OF ORTHOPEDIC BED.

Tuberculosis of the Hip.—Fixation of the joint is indicated for the relief of pain and muscle spasm. The patient is placed on a Bradford frame, and the affected hip is held in the line of deformity by an inclined plane. Traction is applied by means of a padded cuff around the knee and ankle; these are connected with buckles and straps along the legs. A second set of snaps and buckles connect the ankle cuff to the traction apparatus at the end of the bed. For the average child a pound for each year of age is usually sufficient weight. When the patient is turned on his stomach the traction is removed and the incline is then placed in the opposite direction. Abduction, adduction and rotation are corrected by means of a side-working extension that grips the leather cuff above the knee and fastens on a roller that runs along the side of the bed. After the flexion deformity, if present, has been reduced, the hips are placed in hyperextension by placing a small hard pillow under the hips. As the muscle spasm diminishes, the inclined plane should be lowered and the abduction or adduction deformity correspondingly corrected until ultimately the limb is straight in full extension. With the disappearance of pain and improvement in general condition, daily exercise in setting the muscles of the thigh and bending the knee while lying on the affected side should be instituted. After discharging sinuses have healed, or when, in their absence, the general condition and X-ray picture reveals cessation of the active process, active motion of the affected joint should be carefully encouraged, beginning with a very limited arc in rotation when the patient is lying on the affected side. In this way the degeneration of specialized articular structures due to atrophy of disuse can, in large measure, be overcome. The traction should be gradually removed, pound by pound, and entirely dispensed with when its disuse does not provoke the return of symptoms.

Tuberculosis of the Knee.—The method of treatment is determined by the stage of the disease. In the acute stage, without deformity of the affected knee, a posterior splint with traction in full extension is indicated, and recumbency on a Bradford frame should be rigidly enforced. Deformity can thereby be prevented, but once it has occurred traction should be applied at or beyond the angle of flexion which exists. Whereas in hip the traction pulls above both the knee and the ankle, in the case of the knee the pull is only from above the ankle. Subluxation of the tibia is prevented by placing a pad underneath the head of the tibia and corrected by placing the leg on a splint suspended with rubber bands. After the knee is straightened the whole limb is placed on an incline made of board or pillows to avoid equinus. Fixation of the extremity should be maintained until the acute inflammation subsides, and in all cases it should be gradually removed in the following manner: The weight should be diminished by a half pound each week. With continued improvement the weight may be entirely removed for ten minutes each day, and, with the patient placed on the affected side, the leg may be actively flexed and extended through a small arc. This range of motion can be cautiously increased as the recovery of the joint permits. In case the articular surfaces have been destroyed and the joint space obliterated, such procedure is not indicated. With extensive destruction of specialized structures, such as the semilunar cartilages, cruciate ligament and periarticular ligaments, restoration of function is hopeless and resection may be indicated.

Tuberculosis of the Foot.—Strict recumbency and immobilization are indicated regardless of the extent of the involvement of a tuberculous ankle. Equinus deformity should be prevented by the immediate application of a posterior splint. If such deformity exists on first examination, gradual correction can be accomplished by the application of successive splints, each of which tends to bring the foot near a right angle. A splint employed by Rollier has a mobile sandal which allows progressive straightening when equinism accompanies tibiotarsal arthritis. It is generally agreed that heliotherapy is the mainstay for conservative treatment of tuberculosis of the tarsus. Fitzsimmons states that heliotherapy definitely aids before, as well as in the presence of, sinuses. As the acute symptoms subside, motion should be attempted through a small arc, with great caution, and never in any instance should this practice be pursued in the presence of muscle spasm, pain or other indication of an active inflammatory process. Abscesses should be treated as described under tuberculosis of the spine.

Tuberculosis of the Shoulder.—Fortunately, tuberculous disease of the shoulder joint is not common; only three cases occurred in the total of 414 admitted to the J. N. Adam Memorial Hospital between 1913 and 1920. No special immobilization or traction is used unless there is considerable displacement, in which case weights are hung from a leather cuff fastened just above the elbow. The weight of the arm itself, which acts as a natural tractor, is usually sufficient in these cases. Immobilization for the relief of pain and muscle spasm is essential. When such indications of inflammation have subsided, carefully graduated exercises should be instituted for the restoration of function.

Tuberculosis of the Elbow.—This condition is more frequent but less common than involvement of joints in the lower extremity. Immobilization should be discontinued as soon as the acute inflammation subsides. The joint is immobilized in half flexion by means of a wire or celluloid splint open in front. It is joined at the elbow and includes the hand in slight radial flexion.

Tuberculosis of the Wrist and Hand.—The wrist and hand joints are more frequently involved than any other joints of the upper extremity. There is no method of treatment which promises less deformity and greater restoration of function than heliotherapy in conjunction with adequate orthopedic supervision. From the onset it is essential to recognize the potential volar displacement of the wrist which results in a deformity of the hand in the weakest position. In its worst stage, the contraction of the flexor muscles, which accompanies this deformity, may also completely prevent the prehensile function of the hand. A splint should be applied to the volar surface of the forearm and extend along the ulnar surface of the hand as well as along the palm. In this way the tendency toward both ulnar and volar flexion can be overcome, and, if present, these deformities may be corrected by the application of successive splints with gradual correction. Long-continued immobilization is contra-indicated if restoration of function is anticipated. The same precaution should be taken in the removal of the splint and the institution of exercises, as urged in the case of other articulations.

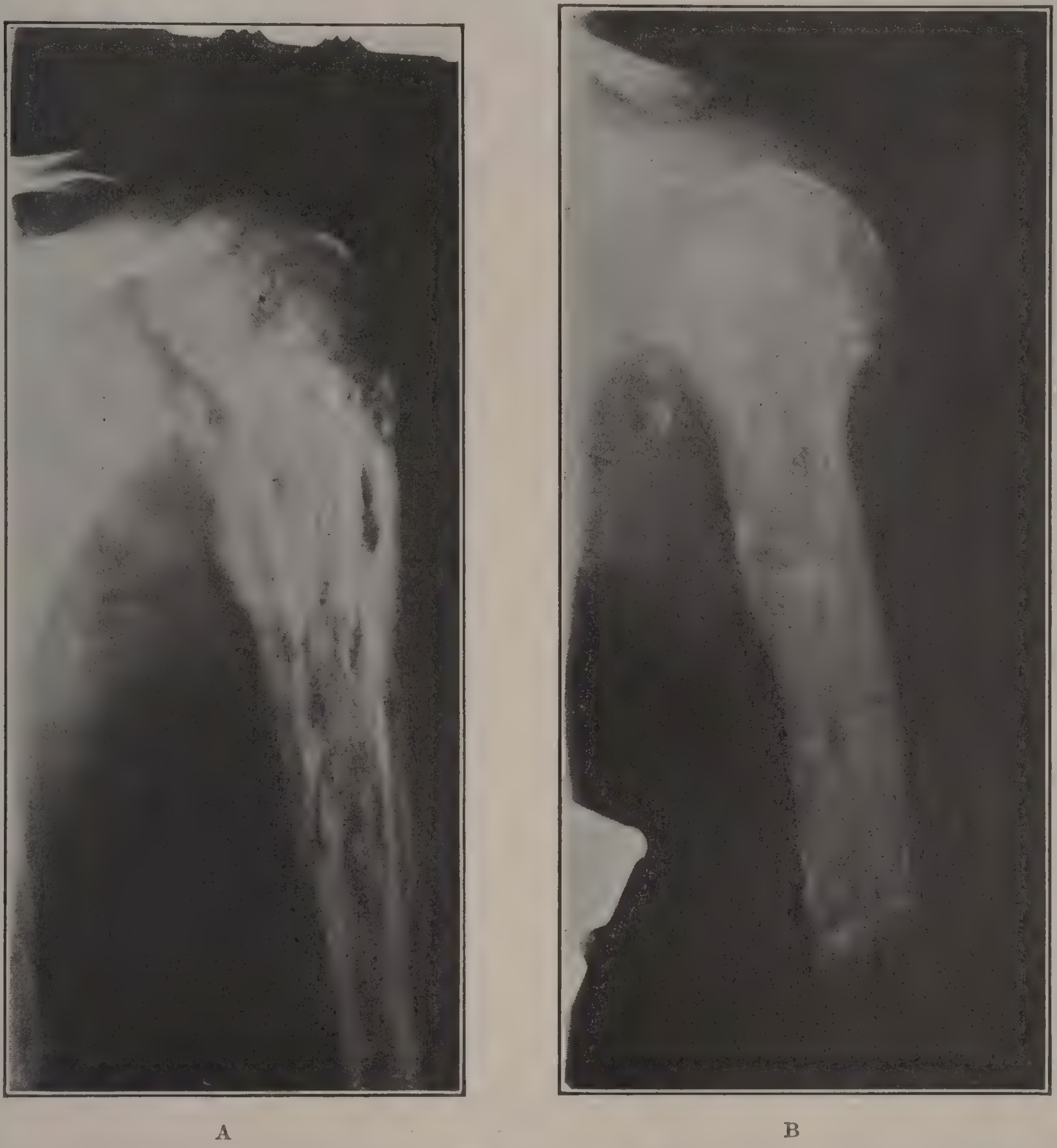

A B

Fig. 4.—Osteomyelitis of Shaft of Humerus. A, X-ray before treatment. B, X-ray three years later.

Dactylitis.—Dactylitis usually responds quickly and permanently to the therapeutic effects of the sun's rays. In this condition, surgical intervention is never justifiable, and it is seldom, if ever, indicated in usual cases of joint tuberculosis described above.

A bed recently devised by LoGrasso for use in orthopedic cases is divided into sections so that the use of pillows for prevention and correction of deformities will be unnecessary. Its ease of operation adds to the comfort of the patient. Wind protection is provided for by means of special appliances. The bed coverings are maintained in position without interfering with the orthopedic apparatus.

Sinuses and Ulcers.—The only surgical interference that would seem to be indicated is aspiration. Occasionally when the pus is very thick recourse may be had to the use of a very narrow-bladed knife. A healthy part of the skin is always chosen for the aspiration or incision to avoid the possibility of a sinus. After the aspiration or evacuation of the pus, a slight pressure with a piece of gauze is applied to prevent bleeding into the abscessed cavity. Dr. Rollier condemns any and all surgical interference except aspiration. There are times when surgery is advisable, but even then it should be judiciously combined with heliotherapy. The operation should be delayed until the sun has had a chance to do its work, not only on the affected part but on the general condition of the patient, thus assuring a more favorable result. Many instances have been seen in which a few months of sun cure have changed the whole aspect of cases which at first had appeared hopeless. Dr. Rollier's writings seem to give the impression that the sun can restore motion in any joint even where there has been considerable destruction and ankylosis of long standing. The experience of others has not always borne out this result, but there is no method that will do more for these cases than heliotherapy under careful orthopedic supervision.

In *peritonitis* the patient is kept in bed until all sinuses have been healed and there is no more evidence of fluid present.

In *tuberculosis of the genito-urinary tract,* if there is a marked cystitis, absolute rest in bed must be insisted upon.

In *tuberculosis of the lymph-nodes* no bed treatment is required outside of the three or four hours of the sun treatment, unless it is indicated by poor physical condition.

The same may be said in cases of *tuberculosis of the eye, rib, face* and *upper extremities.* Only moderate exercise is permitted even with our best cases.

It is the opinion of most of the men who are employing heliotherapy that sun cure is not only useless but even harmful for *pulmonary tuberculosis.* This was doubted by those in charge of the sun treatment at the J. N. Adam Memorial Hospital, and, to test the truth of the contention, during the summer of 1922 fifty moderately advanced and advanced cases with positive sputum who were unimproved or progressive were placed under sun treatment. Notwithstanding the nature of the cases selected, the results were so satisfactory that it is the intention to extend the sun treatment to practically all of the pulmonary cases in the institution. A diminution of temperature was noted soon after sun treatment was started in all of those cases with elevation of temperature. The cough lessened and expectoration greatly diminished soon after treatment and the general physical condition improved markedly. There were no hemorrhages in any of these cases although several of the patients had repeated hemorrhages previous to the institution of the treatment.

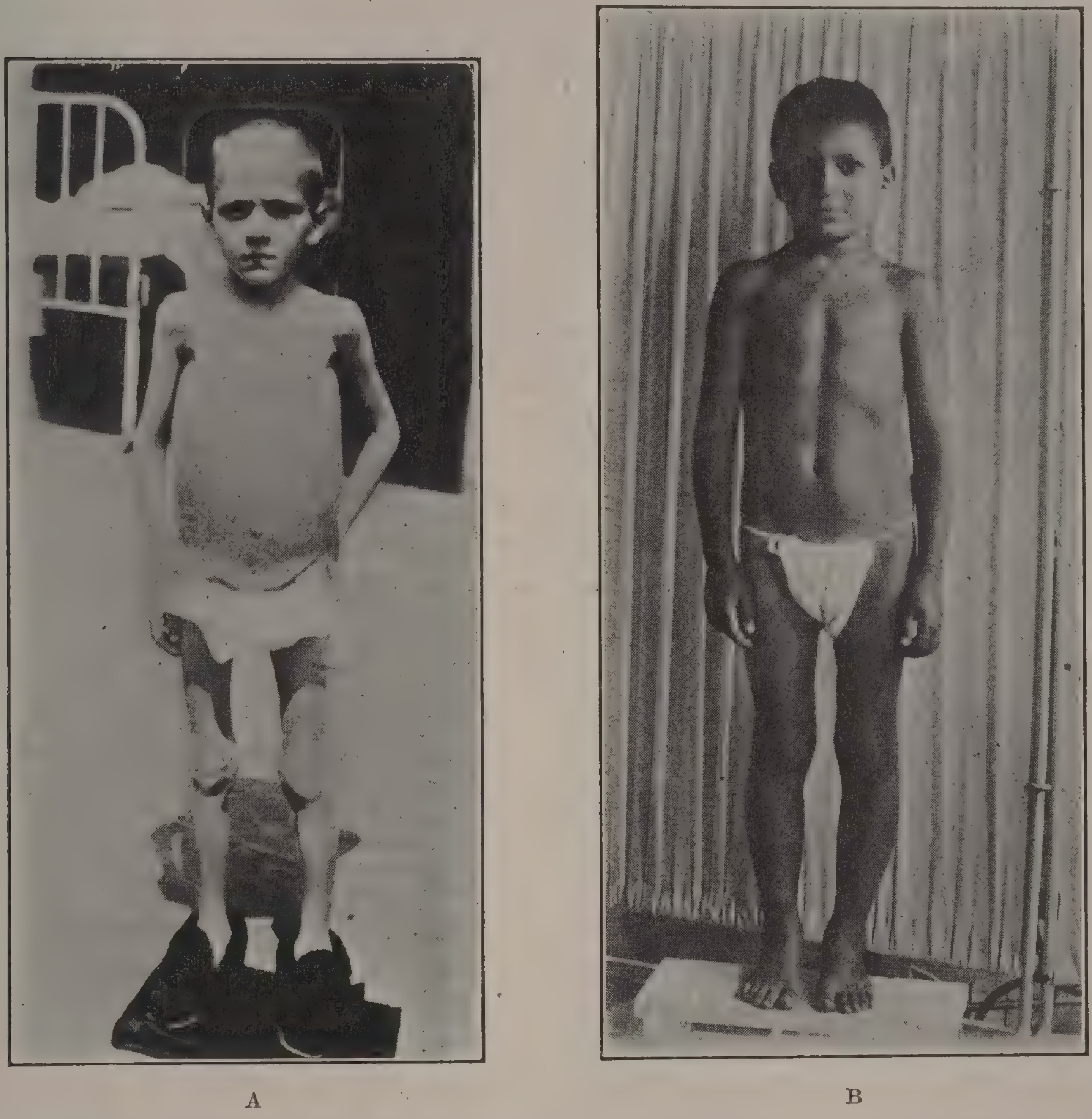

A B

FIG. 5.—TUBERCULOUS PERITONITIS. A, On admission. B, One year later.

It would seem that the unsatisfactory results that have been reported in the treatment of this type of tuberculosis by heliotherapy were due to the fact that the sun was given too intensively and at a time when the heat was very depressing, that is, at meridian. If the early morning or late afternoon is chosen for the treatment, the unfavorable results, such as rise of temperature, hemorrhages and reactivation of the disease, will be avoided. It has been noticed also that in a large number of pulmonary cases where leukocytosis was marked, due in all probability to mixed infection, the blood picture returned to normal after two or three months of sun treatment.

The Thezac-Porsmeur lens may be used in conjunction with the general exposure for stubborn sinuses and ulcers with very beneficial results. The light transmitted by this lens contains practically none of the very short wave-length frequencies but is exceedingly rich in the long heat-producing wave-lengths, especially the red rays of the visible and infra-red rays of the invisible spectrum. It is a bi-convex lens, 12 inches in diameter with a focus of 72 inches. It is so focused on the lesion that it forms a circle of from 6 to 8 inches in diameter. The rays are thus focused for five minutes the first day and the period is gradually increased each day until an hour or two of exposure is reached. This lens has also been found very useful in alleviating pain.

Pain has also been relieved by the use of heat. A cradle which carries twelve 40-watt tungsten lamps is placed over the patient and covered by the bedclothes. Any four or all of the lights may be turned on at one time, and the light thus applied for thirty minutes to one hour twice daily. A cool compress should cover the forehead, plenty of water should be available for the patient and a tepid bath should be given when the heat is discontinued.

The disfiguring scars which often remain after healing has taken place are bleached and made smoother by the use of blue light, wave-lengths 400 to 510. This portion of the spectrum has also been found to be very beneficial in the treatment of acne.

The question has been asked what proofs we have for claiming that the results obtained in tuberculosis are due to the sun rather than to the absolute rest in bed and exposure to the air which are part of the treatment by heliotherapy.

It has been noticed in the ten years during which heliotherapy has been carried out at the J. N. Adam Memorial Hospital that throughout the winter months, when sun cure is practically discontinued, both the general physical and local conditions of the patients are at a standstill, if not retrogressing. As soon as the sun cure is reëstablished, there is a sudden improvement both in their general and local condition. These improvements are noted by a lessening of pain, decrease in the discharge and diminution of the size of the ulcer.

These cases that show no improvement in the winter, aside from being exposed to the sun, receive the same treatment and are handled in the same way as they are during the summer when they are taking the sun treatment. During the summer we have restricted some of our patients to ordinary intensive hygienic treatment, plus absolute rest in bed, and the results in these cases have not by any means compared with those obtained by the Rollier methods of heliotherapy.

As recovery with sun cure is necessarily a rather slow process, the prolonged treatment often reacts upon the mental attitude of the adult patient and that doubtless is why the best results are had among the children. Fortunately, deep X-ray therapy promises to shorten the duration of the sun cure by one-third to one-half. At present a special building for X-ray therapy is being constructed at the J. N. Adam Hospital and intensive treatment will be begun soon as an adjuvant to heliotherapy.

A great deal has been written about artificial means of light therapy. At their best they are but poor substitutes for the sun's energy. Solar therapy consists not only of exposure to the sun for two or three hours but also of absolute rest in bed, fresh air and proper hygienic surroundings.

For the past seven years, during the winter months when the sun has not been available, the Alpine Sun Lamp has been used at the J. N. Adam Memorial Hospital. The results in superficial lesions have been somewhat satisfactory but the favorable general results that have been lately reported by others have not been noted.

The past winter the carbon arc light has also been used at the above-named institution but, because of the limited number of patients treated, a report of the results has not yet been made.

Kisch, Bier, Gerhartz, Rieder and Nagelschmidt have been inclined to the belief that cures were effected by hyperemia, and the changing of a passive congestion to an active one. Their results were obtained by using lights rich in the heat rays of the spectrum. In this connection it is interesting to note that Bier and Kisch have used as adjuvants to heliotherapy Bier's hyperemic technic and the administration of sodium iodid.

Statistics

Dr. Rollier's statistics show a very high percentage of cures, but, since his classification of results of treatment is not definitely stated, it is impossible to make a fair comparison between his results and those obtained in American institutions. In the compilation of the statistics of the J. N. Adam Memorial Hospital, where heliotherapy is extensively practiced, an exact definition of the terms "apparently recovered," "arrested" and "improved" has been established.

To be classified as:

1. "Apparently recovered," the patient must be free from all symptoms with sinuses closed and ulcers healed, and be up and about for at least six months previous to the date of discharge. This applies to disease of bone, joint or kidney. With involvement of the peritoneum, glands,

epididymis, skin or other soft parts a period of only three months is required.

2. "Arrested," there must be no symptoms, sinuses and ulcers being healed or showing no activity while the patient may be up and about or in bed.

3. "Improved," the patient must show definite evidence of improvement of symptoms and signs.

With this rigid definition of terms, the slight discrepancy noted in comparing the following statistics with those of Rollier is readily accounted for and on the whole the results compare very favorably with his.

Seventy-eight per cent of the adults and 18 per cent of the children discharged showed a pulmonary lesion.

Fourteen per cent of the bone and joint cases in adults and 21 per cent in the children had multiple lesions.

Fifty per cent of the bone and joint cases in adults and 44 per cent in children had sinuses and secondary infection.

Thirty-six per cent of the bone and joint cases in adults and 27 per cent in children had had surgical interference.

Seventy-six per cent of all of the joint cases were discharged with partial or full motion.

The average duration of illness of all of the bone and joint cases before admission was two and one-half years.

The deaths among the gland cases were due to causes other than tuberculosis.

Of the 3 cases of Pott's disease, 2 died of influenza during the epidemic and 1 had a psoas abscess rupturing into the intestines, causing death within a few days.

The knee and epididymitis cases also died of influenza during the epidemic. The two hip cases were far advanced, of several years duration and showed amyloid changes.

A large number of the unimproved cases were in an advanced stage of the disease and practically all had sinuses and secondary infection. Some showed amyloid changes.

Many of the arrested and improved cases, if they had remained long enough to have met the time requirements of the classification, might have been discharged as recovered. As soon as a patient feels well and is allowed to be up and about, he is likely to become restless and anxious to go home. This restlessness is increased by the imprudent remarks of friends and relatives who judge only from outward appearances. A little better judgment and more perseverance on the part of both patient and family may assure better results.

It has been clearly proved that solar radiations can be successfully applied not only in tuberculosis, but in cases of puerperal sepsis, anemia, Results of Heliotherapy in Tuberculosis from 1913 to 1922 in All Cases Which Remained in J. N. Adam Memorial Hospital over Three Months

(Average Length of Stay, 12 Months, 27 Days)

	Glands	Peritonitis	Spine	Hip	Sacro-iliac	Knee	Ankle and Foot	Shoulder	Elbow	Wrist and Hand	Humerus	Femur	Ischium	Sternum	Osteomyelitis	Kidney	Epididymitis	Eye	Lupus	Total
Apparently recovered	244	63	16	35	0	13	13	0	4	15	0	2	1	2	8	4	6	15	2	443
Per cent	83	81.8	32	60.4	0	46	72.2	0	57.1	78	0	50	100	66 2/3	50	16.4	66.6	93.7	50	66.5
Arrested	28	10	14	11	2	9	3	3	3	4	1	1	0	1	6	13	2	1	1	113
Per cent	9.14	12.9	28	18.9	100	32.1	16.5	100	42.8	21	100	25	0	33.3	37.5	54.4	22.2	6.25	25	16.9
Improved	18	0	8	7	0	3	2	0	0	0	0	1	0	0	2	4	1	0	1	46
Per cent	5.8	0	16	12	0	10.5	11	0	0	0	0	25	0	0	12.5	16.4	11.1	0	25	6.9
Unimproved	4	4	9	4	0	2	0	0	0	0	0	0	0	0	0	2	0	0	0	25
Per cent	1.4	5.1	18	6	0	7	0	0	0	0	0	0	0	0	0	8.2	0	0	0	3.7
Dead	4	0	3	2	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	8
Per cent	.4	0	6	3.4	0	3.5	0	0	0	0	0	0	0	0	0	4.1	0	0	0	1
Total	294	77	50	59	2	28	18	3	7	19	1	4	1	3	16	24	9	16	4	635
Per cent	44.1	11.5	7.5	9.3	.3	4.2	2.7	.4	1	2.8	.15	.6	.15	.4	2.4	3.6	1.3	2.4	.6	100

rickets, osteomyelitis and non-healing wounds, and in convalescence from all wasting and infectious diseases. This is particularly true of osteomyelitis and rickets. Osteomyelitis, although less amenable to treatment than tuberculosis, has more often responded favorably to heliotherapy than to surgical interference.

Recent studies of rickets have shown that, while a deficiency in the calcium or phosphorous content of the diet undoubtedly contributes largely to the pathogenesis of the disease, the lack of sunlight is also a contributing factor and one that must not be overlooked; and it has been demonstrated that not only can rachitic symptoms be averted through exposure to the sun's energy, but cures can be affected after the disease already exists.

The treatment of these other diseases by heliotherapy is mentioned in the hope that such a unanimity of opinion will be created between the medical profession and the laity as will demand that there be established in connection with every general hospital a center in a suburban district at which patients may share in the healing qualities of the sun and the invigorating influence of fresh air.

In conclusion it cannot be too firmly asserted that heliotherapy, in preventive and curative medicine, must be accepted as one of the most effective agents at the command of the modern therapeutist and clinician. Its specific value in tuberculosis, rickets and the up-building of resistance and general physical condition is known. Its further extension in the field of therapeusis is merely conjecture but with a greater knowledge of its action upon physiological and pathological processes its application will be increased and rendered more efficient.

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CHAPTER XXVI

LEPROSY

RICHARD P. STRONG

TREATMENT

General Treatment.—As soon as the diagnosis of leprosy has been carefully made, it is important that the patient should be placed in hygienic surroundings, and that these be made as attractive for him as possible in connection with his isolation. In order that the feeling of isolation may be alleviated as much as possible, it is usually better to allow him to associate with other individuals suffering with leprosy. Obviously this can best be accomplished in properly arranged leper colonies or institutions devoted to the care of lepers. He should be placed upon a sufficiently abundant and nourishing diet. Thorough cleanliness and hygiene of the skin should be maintained, and clean underclothing frequently supplied. Pediculosis, scabies, ring-worm, infection with Demodex folliculorum, and other cutaneous disturbances should be eliminated by proper treatment. Frequent bathing is advisable and sodium bicarbonate may often be added to the warm bath for its cleansing properties. Certain natural baths in Japan were formerly thought to possess curative properties, and in Hawaii the aromatic leaves of the eucalyptus tree were formerly placed in the baths. It seems improbable, however, that any medicament employed in the bath has any special therapeutic property.

The leper being generally looked upon as an outcast from society, and usually shunned by most people, is often apt to have fear of the discovery of his condition, and, after his isolation, to brood upon it. Sometimes he assumes a hopeless attitude regarding his cure. As a result he often becomes exceedingly mentally depressed, and this mental attitude may affect his desire for food and his powers of assimilation, and hence his vitality and resistance to the infection may further suffer. Therefore, attention to the mental condition is necessary and an attempt should be made to encourage the patient and to keep him from brooding over his unfortunate state. For this reason it is important that suitable and, if possible, entertaining work be provided for him, and in all leper institutions it is advisable to keep every leper employed according to his capacity for work, even though some can do very little. Healthy outdoor employment if not too strenuous may be beneficial toward recovery from the disease. Various industries, agriculture and dairy farming related to the needs of the leper institution may be indulged in by many of the patients with less advanced lesions. The establishment of a school, or a band of music, theatrical performances, etc., are also of importance. An attempt should be made to have the leper lead as nearly as possible a natural life and to encourage him to forget his unfortunate condition, and to feel that he is a useful member of the leper community in which he dwells. How much can be accomplished in this respect may be seen from a visit to the Government leper colony in the Philippine Islands which occupies the beautiful island of Culion. Here there have been collected since 1906 more than 12,000 lepers. The lepers are given all possible liberty, and to a large extent are controlled by regulations which they themselves make. They are allowed to punish offenders against their own regulations. They are privileged to elect their own mayor and councilmen. A police force composed entirely of lepers has been organized, and it is its duty to see that the town is kept in good sanitary condition as well as to make arrests of offenders against their own ordinances. Each councilman is responsible for the proper housing, good order, and adjustment of complaints of the people in the section of the town which he represents. The question of lepers contributing something toward their own support has received most careful attention, but on closer consideration it has been found that not much assistance in this direction can be expected. A store has now been started at which anything produced by a leper may be sold. There is also kept for sale a stock of such things as the lepers may wish to buy. This store is beginning to exert a very favorable influence. For example, nearly a ton of fish is offered for sale by the lepers every day. Milk from the goats and special vegetables may now be obtained for the sick. In connection with the store there is a post office, with a leper postmaster in charge. All outgoing mail is disinfected. When it is ready, a non-leprous employee collects it and places it aboard the mail-steamer. A special currency has been coined for the exclusive use of the lepers. The denominations are the same as those of the regular Philippine currency. If a leper has occasion to send money out of the colony, he can purchase a regular money order from a non-leprous clerk, who mails it for him.

Bodaan has also recently described the conditions of a leper village settlement in Java where voluntary isolation is carried out, which presents a good example of what con be done for lepers by tactful and sympathetic treatment.

As in all chronic wasting diseases, the diet constitutes a most important feature in the treatment of leprosy. The waste of the tissues must not only be built up, but the strength of the patient and his natural resistance to infection must be conserved as far as possible. Hence it is important for the diet to be of a proper nature and properly prepared as well as nutritious, and sufficient in amount in proteins, fats, carbohydrates and vitamins. Fresh meat, vegetables, fruit, and dairy products have a very important place in the diet of lepers. Although it has been suggested that fish should be avoided, there appears to be no definite evidence that fresh fish has any unfavorable effect on the disease. Dutton points out that, when the food supply consists mainly of fish or of salted fish, a deficiency of some element of diet may occur, and that no fish except shellfish contains carbohydrates. Underhill, Honeij and Bogert have pointed out that when leprous patients are given calcium they tend to retain it to a very marked degree, and they suggest that plenty of calcium should be supplied in the food as a therapeutic measure. Every effort to improve the general condition of the patient should be made, and particularly on this account a careful examination of the stools for intestinal parasites should be carried out and any parasites found present should be eliminated as far as possible by proper treatment. Ankylostomiasis and other intestinal parasitic infections are very common among lepers. Malaria and syphilitic infection should also be sought for, and if either is present treatment with quinin or arsphenamin, as the case may be, should be administered. In this connection it should be borne in mind that many lepers will give a positive Wassermann reaction even in the absence of coexisting syphilis. Either syphilis or tuberculosis may be associated with leprosy in the same patient. Constipation or diarrhea or dysentery during the disease may also require special and proper treatment.

When attention has been given to these details of treatment as outlined above, and the patient has been placed in favorable surroundings and given proper diet and kindly care, many cases begin to improve without specific treatment. There is often an improvement in the general nutrition, a gain in weight, and sometimes even an improvement or disappearance of the lesions of the skin. Also the mental condition of the patient frequently becomes better, this feature being no doubt sometimes influenced by the fact that he no longer fears the detection of his ailment. However, usually this improvement is only temporary, and fresh exacerbations of the disease occur. A number of references are found in the literature to the spontaneous recovery of cases of leprosy. If specific treatment is given, which subject will be discussed presently, the visible lesions may also disappear entirely, and after a considerable period the leprosy bacilli may no longer be found in the excretions. McCoy who has had a wide experience with the disease, states that, when asked about the curability of leprosy, he usually answers that he has seen a number of cases of recovery, but doubts if he has ever seen one cured. Throughout the course of treatment and observation of the patient it is important that he should continue to observe the general rules of health. Relapses after long periods of quiescence are frequent. If diet, work in the open air, rest, and sanitary surroundings are neglected, and the resistance of the patient lowered thereby, the lesions and symptoms of the disease often reappear. We do not know whether climate plays any part in relation to treatment, and we can only say that in some localities the disease shows no tendency to spread, while in others it does. Whether these differences are dependent upon temperature and moisture seems doubtful. Iodid of potash, mercury, strychnia, arsphenamin, and a number of other drugs have been recommended for the treatment of leprosy, but they have not been proved to have much curative value.

Surgical Treatment.—Surgical treatment of leprosy is not infrequently required. Patients with respiratory obstruction due to nodules or ulcerations which may cause contraction of the larynx often suffer intense agony. The performance of tracheotomy for the relief of such laryngeal stenosis is not infrequently required. The results are usually very satisfactory and wonderful relief is often given the patient. Muir recommends that the operation should be done with local anesthesia, the subcutaneous tissues being perfused with 3 c.c. of a ½ per cent eucain solution, containing about ½ c.c. of a 1:1,000 adrenalin solution, there being practically no bleeding when this solution is employed. Under the influence of the rest obtained by the insertion of the tracheal tube, the infiltrated and ulcerated vocal cords may return to a considerably more normal condition. In some cases the tube may be dispensed with after a few weeks, while other cases wear it for years without serious inconvenience.

In perforating ulcer of the foot and toes, the condition is often associated with necrosis of the bone. Some of these ulcers will persist for years, even with rest and careful dressing, unless the necrosed bone is removed. The removal of sequestra from bones of the hand or of the feet, or in some cases the amputation of fingers or toes, or even of the entire hand or foot, may be advisable. Chronic ulcers with a hard fibrous base are often scraped with advantage and the hard fibrous tissue dissected out. The surgeon should bear in mind that a certain amount of leprotic fever may follow an operation where a large amount of leprotic tissue containing many leprosy bacilli has been cut through. Sometimes after such fever there may be an improvement in the condition of the patient, or on the other hand the case takes an unfavorable turn. Disfiguring leprotic lesions may be sometimes removed for purely cosmetic purposes. When a lesion is well circumscribed, it may appear advisable to excise it or to cause its destruction by the application of carbon dioxide snow. In general it may be said that wounds in lepers usually heal as promptly as they do in other individuals. While general anesthetics are well borne, they are often not needed. Local anesthetics may be employed, and in many instances the analgesia associated with some forms of the disease permits of surgical operation without inflicting pain on the patient. Goodhue has shown that great improvement in the appearance of the patient can sometimes be effected by the removal of disfiguring large nodules on the face and other parts of the body. Stretching of nerves has been practiced for the relief of intractable neuralgia, but the results are often disappointing. Certain symptoms connected with the eyes may also require surgical intervention. Thus Muir points out that where ectropion has been caused either by trophic changes, paralysis of the orbicularis, or the contraction resulting from the absorption of nodules, plastic operations will restore the protective function of the eyelids as well as remove the disfigurement. Where iridocyclitis has resulted in high pressure in the anterior chamber of the eye, great relief will at once be given by the administration of cocain and tapping of the anterior chamber by the insertion of a Graefe knife at the outer side of the corneosclerotic junction. Later if the transparency of the cornea has been impaired by the keratitis an iridectomy may be performed.

Local Treatment.—Local treatment of the leprous lesions with many substances has been attempted. Among those which have been particularly used recently may be mentioned chlorid of zinc, trichloracetic acid, basic fuchsin and carbon dioxide snow. The freezing with carbon dioxide snow has been extensively employed but it is somewhat painful and many patients strenuously object to it. It has been advised that the freezing should be done once a week or once in ten days, depending largely upon the time required for the healing of the abraded surface. Obviously its use is most desirable or only desirable where isolated lesions exist. It is sometimes employed with good results where large circumscribed nodules of this nature are present.

Minett has recommended benzoyl chlorid in petroleum oil as a nasal spray or paint which he believes may sometimes render the discharge from the nose free from bacilli.

X-rays have been used fairly extensively and usually cause improvement in the local lesions exposed to their action and often, as well, of the lesions situated elsewhere on the body. The most beneficial effect on the lesions is sometimes observed after slight burning of the skin by the rays. The writer has seen many cases of leprosy treated with X-rays, but has never seen a case cured by such treatment. Its continued employment is probably dangerous. When one considers the general infection which exists in leprosy, one could hardly expect that the disease would be cured by such a procedure. Radium treatment has also been recommended, but as yet we have no definite evidence of its efficacy.

Specific Drug Treatment.—Of the various drugs that have been recommended for the treatment of leprosy, the most favorable results have apparently been obtained with chaulmoogra oil and its derivatives. Chaulmoogra oil is obtained from Taroktogenos kurzii which is found in the

Assam valley and the Chittagong hill tracts in India. Brill has shown that the oils from three species of hydnocarpus, kurzii, wightiana, and venenata, are practically indistinguishable chemically from true chaulmoogra oil. However, that extracted from Gynocardia odorata differs considerably from the others and contains neither chaulmoogric nor hydnocarpic acids which are present in the other varieties mentioned. The various species of hydnocarpus are found in South India, Ceylon, Burma and Siam, while Hydnocarpus alcalæ is found in the Philippine Islands. It is important to collect the fresh seeds, and the oil is obtained usually by cold expression, but sometimes hot expression is used.

Buddhist records of centuries ago are said to refer to the improvement of cases of leprosy after the ingestion of the chaulmoogra seeds. Manson, in the first edition of his textbook on tropical diseases published in 1898, says that chaulmoogra oil in doses of from 2 to 10 up to 40 drops or more, according to tolerance, given three times a day, together with inunctions of the same drug mixed with some oil, has always been a favorable remedy with English practitioners for the treatment of leprosy. In the United States, Dyer, Blanc, Heiser, Hopkins, Connell, McCoy and Hollman have particularly advocated its use. When given by the mouth, it frequently causes gastric disturbances and a number of patients are unable to take it on this account while others become accustomed to it in a short time. When given by the mouth the oil is probably best administered in gelatin capsules. McCoy recommends, to begin with, a dose of 5 minims (0.3 c.c.) after each meal, and increases the dose rapidly to the point of tolerance. Some patients can take as much as 300 or 400 minims (17.75 to 24 c.c.) daily. In order to avoid the gastro-intestinal disturbances, it has been suggested that the oil be combined with other substances and given by subcutaneous or intramuscular injections. To facilitate its absorption, Heiser and Mercado combined it with the resorcin formula of Unna. They have recommended for injection, chaulmoogra oil 60 c.c., camphorated oil 60 c.c., resorcin 4 gm. The ingredients are mixed and dissolved with the aid of heat on a water bath and then filtered. It is recommended that the injection should be made in the gluteal region at weekly intervals in ascending doses, 1 to 5 or 10 c.c. Jeanselme recommends for injection 1 part chaulmoogra oil, which has been washed with alcohol, filtered through cotton, and sterilized at 100°C., to which is added 1 part of a mixture of guaiacol 50 cg., camphor 25 cg., and oil of vaselin, sterilized and filtered, 5 gm. The dose of this preparation may be 2 c.c. twice a week and increased rapidly to 10 c.c. twice a week.

The hypodermic or intramuscular method of injection, however, also has its disadvantages. The injections are often painful, and abscesses are not rare even when scrupulous care is exercised in the technic of administration. The patient may manifest indications of severe cardiac and respiratory disturbances immediately after the injection is given, and deaths have been reported as apparently due to embolism. Vahrem has reported on a preparation of a "pseudocolloidal" emulsion of chaulmoogra oil with gum arabic, suitable for intravenous injection, and cites cases favorably treated with no unfavorable reactions and no disagreeable effects. He recommends for the first injection ¼ c.c., progressively increased by $\frac{1}{10}$ c.c. until 2 c.c. have been given. In 1916 Rogers prepared soluble salts of fractions of the fatty acids of chaulmoogra oil and employed these both for intramuscular and intravenous injections. The preparations particularly prepared and used were sodium gynocardate, sodium hydnocarpate and sodium chaulmoograte. The second of these salts contained a large amount of hydnocarpic acid and the third a large amount of chaulmoogric acid. The sodium hydnocarpate proved most favorable for use, and it was found that it could be more satisfactorily prepared from hydnocarpus oil then from chaulmoogra oil. Rogers also tested the action of other oils with a large content of unsaturated fatty acids, particularly cod-liver oil, soy bean oil, and sardine oil. He found the cod-liver oil preparation containing sodium morrhuate to be very efficient when it was given intramuscularly or intravenously. He concluded that these different oils may be used to considerable advantage in the treatment of leprosy, and that, if a patient ceases to respond to one oil, another one should be substituted. A 3 per cent solution of sodium salts of the fatty acids is supplied in sterile ampules by Messrs. Smith, Stanistrett & Company of Calcutta. Rogers recommends to begin with at least ½ gr. (0.03 gm.) in 1 c.c., and increased by 0.5 to 1 c.c. at a time, until 2 to 2½ gr. (0.12 to 0.15 gm.) in 4 or 5 c.c. is reached, provided severe giddiness is not produced. The injections may be given once or twice a week, and on the other days 2-gr. pills (0.12 gm.) of the drug may be taken by mouth after meals, beginning with three times a day, and increasing by 1 daily until 10 or 12 are taken each day, as long as the digestion is not disturbed or giddiness produced. Some patients are able to take as much as 40 gr. (2.4 gm.) in 20 pills daily with advantage. The injections alone, however, are frequently sufficient, and treatment by the mouth can often be avoided. Subcutaneous injection of the 3 per cent solution causes but little pain and may be necessary when suitable veins cannot be found. The ampules for intravenous injection should contain 0.5 per cent sodium citrate in order to prevent clotting which would render the veins unfit for further injections. Both febrile and local reactions may follow the treatment, and the fever may last for from one to three days, rarely as long as a week. During the fever it seems advisable not to repeat the injection. Rogers found that in the more recent cases of leprosy within three years of onset far more successful results were obtained with this treatment than in cases of long standing of which only 25 per cent cleared up under treatment. Harper of the Makagoi Leper Settlement has reported excellent results from the use of intravenous injections of a mixture of chaulmoogra oil 500 minims, sulphuric ether 500 minims, iodin 1 gr. The mixture is a clear one and when injected intravenously it is said not to cause capillary embolus. The injections are given daily, 10 minims being given for the first three days and 20 minims thereafter. The injections are painless but are said to be likely to produce coughing, especially if there is a disease of the respiratory tract. In January, 1923, Harper reported upon 37 cases of leprosy that had then been given treatment for about two years with intravenous injections of chaulmoogra oil. In July, 1921, he considered that 28 cases had improved, 6 had remained unchanged, and 3 were worse. Between that date and the end of August, 1922, 5 of the cases (all of the purely nerve type) had been discharged from the asylum, 5 had continued to show improvement, 12 were apparently unchanged, and 15 were worse. Altogether he had treated 265 cases by intravenous injections of chaulmoogra oil for periods of from a few weeks to 2 years. The patients had received 40,000 intravenous injections of the oil without any serious mishaps. His results are as follows:

Dead	11,	of whom 5 were very aged
Improved	28,	including 15 discharged from the asylum
Unchanged	195	
Worse	31	
Total	265	

Harper in his last report recommends from 5 to 10 minims of the crude chaulmoogra oil, sterilized by heat, without the addition of any other drugs. This is injected every day except Sunday for three weeks at a time. Then the patient is allowed to rest for two weeks. He believes that this treatment is of value in early cases and is preferable to treatment by sodium gynocardate, sodium hydnocarpate, or sodium morrhuate. Muir reports that he has himself found the following formula most efficient for the treatment of leprosy: ethyl esters of the fatty acids of oil obtained from Hydnocarpus wightiana seeds 1 c.c., pure creosote 1 c.c., camphor 1 gm., olive oil 2.5 c.c. He reports that this mixture can be given hypodermically or intramuscularly without pain.

The ethyl esters and other esters of chaulmoogric acids were prepared in 1904 by Power and his collaborators at the Wellcome Chemical Research Laboratories in London. In 1909 Ludwig Taub obtained patent rights in Germany for the preparation of the esters of chaulmoogra acids and their employment. The preparation was placed upon the market under the trade name of "Anti-leprol." A short time afterwards patent rights were also obtained in Great Britain and the United States. As a result of the war the German patent rights were confiscated, and they were sold in the United States to the Winthrop Chemical Company of

New York, which is preparing and distributing the ethyl esters of chaulmoogra acids under the trade name of "Chaulmestrol." In 1919, Hollman and Dean prepared and used by intramuscular injection the ethyl esters of fractions of the fatty acids of chaulmoogra oil. These were separated by fractional crystallation and then converted into the ethyl esters. Four fractions in all were used, and groups of cases were treated with each. McDonald and Dean have also used the ethyl esters of the fatty acids by the mouth, by inunction and by hypodermic injections. They also suggested the combination of the ethyl esters with 2 per cent of iodin for hypodermic use. In 1919, Hollman and Dean reported results of treatment in 26 cases during a period of less than two years; 8, or 30 per cent, of these became bacteriologically negative within this time. McDonald, in 1920, also recorded the paroling of 48 cases of leprosy, and, in 1921, of 94 more cases, making a total of 150 cases. These patients had been treated with weekly injections of the mixed ethyl ester of chaulmoogra oil with 2 per cent of iodin in chemical combination. One c.c. was given weekly, increasing the dose until 5 c.c. were given every seven days as the maximum dose for an adult. Capsules of the fatty acids of chaulmoogra oil, with 2.5 per cent of iodin chemically combined, were also given by the mouth three times a day. The doses by the mouth began with 1/6 gm. per 100 pounds of body weight, and went as high as 1 gm. per 100 pounds of body weight three times a day. McDonald later reported that he believed the oral administration was by no means necessary and that the rôle of the iodin was probably a minor one.

During 1922, Morrow, Walker, and Miller treated 21 cases of leprosy of the nodular, maculo-anesthetic, and mixed type chiefly with the ethyl esters of the total fatty acids of chaulmoogra oil. The injections were made intragluteally at weekly intervals. They found that the butyl and propyl esters produced much less local reaction and pain than the ethyl esters, and therefore these were substituted for the ethyl esters in the later treatment of the patients. The therapeutic action with these appeared to be as good as that obtained with the ethyl esters. The 21 patients were under treatment for a period of from three to eighteen months with an average of eight months. Of these patients a boy aged fifteen with advanced leprosy died of the disease. One man, aged seventy-one, died of "pneumonia-leprosy" unimproved. Three patients in the advanced stages became definitely worse. Nine showed no improvement. Two patients (cases of moderate severity) were markedly improved. Three (cases of moderate severity) were slightly improved, and, 2 patients with the disease in an early stage ran away after three months' treatment. None of these patients became bacteriologically negative during treatment, but the nasal discharge in 1 case became negative after more than a year of treatment. It appears to be the general opinion that advanced cases of leprosy do not yield to treatment with the ethyl esters, but that the early cases are frequently benefited by them. In a recent report of our Public Health Service it is stated with reference to the use of the ethyl esters of chaulmoogra oil in the treatment of leprosy that they may be regarded as the most valuable therapeutic agents in the treatment of this disease which have been developed up to the present time. Attention is also called to the fact that they are superior to chaulmoogra oil in that they may be administered practically to all patients, and that when injected subcutaneously their use is not accompanied by the pain and discomfort or slow absorption and frequent abscess formation attendant on the use of crude chaulmoogra oil. Up to the time that the Public Health Service report was made (November, 1921) of the patients treated with the ethyl esters and paroled from the two leper institutions in Hawaii as apparently cured, 8 per cent had relapsed and been returned to these institutions for treatment.

Marchoux has recently reported on 4 cases of leprosy treated by intravenous injections with sodium morrhuate and sodium gynocardate in doses similar to that employed by Rogers. In none of the cases was any benefit noted. These observations were also controlled by animal tests in relation to rat leprosy caused by intraperitoneal injection of cultures. Here again the drug seemed merely to aggravate the symptoms and not to lead to their amelioration.

Tucker and Horwitz of the Palo Seco leper colony, Panama, report that about 78 patients are at the present time being treated by weekly intramuscular injections of the ethyl esters of chaulmoogra oil. The results that are being obtained, though varying considerably with the individuals, are reported as rather gratifying. The time that the patients have been under treatment, however, according to the report, precludes the formation of a definite opinion as to the final outcome of the cases. In Para, Brazil, some thousand lepers have also been treated with the chaulmoogra oil. Over 16,000 injections have been reported up to March 31, 1922, but the number cured is not stated.

In the Philippines recently 76 cases of leprosy were divided into 5 groups and treated with 5 preparations as follows.

1. Sodium gynocardate "A" (the hydnocarpate of Rogers).
2. Sodium gynocardate "S", the sodium salts of the fatty acids of chaulmoogra oil.
3. Sodium morrhuate, the sodium salts of the total fatty acids of cod-liver oil.
4. Chaulmoogra emulsion "S" (or Collobiasis substitute); an emulsion containing chaulmoogra oil and acacia.
5. Mercado mixture, of which the formula is: camphorated oil 10 per cent, and chaulmoogra oil, āā 60 c.c., resorcin 4 gm., purified ether 2.5 c.c.

The first three preparations were given by the intravenous route, the last two by the intramuscular or the subdermal, while in some cases these methods were combined. The first three were given in doses starting with 0.5 c.c. and increasing by 0.5 c.c. at a time up to 12 c.c. (morrhuate) or 15 c.c. (gynocardate "A" and "S"). The Collobiasis was given, as a rule, in 2 c.c. doses, while the Mercado mixture, from an initial dose of 0.5 c.c., was raised to a maximum of 8 c.c.

Of these preparations, gynocardate "A" was found to give the least severe reactions and to lead to the best results, 86 per cent of the cases showing some degree of improvement. The gynocardate "S" gave but little constitutional reaction, but at times led to considerable pain during injection; 60 per cent of cases were more or less improved. Sodium morrhuate, as noted elsewhere, was found in the Philippines also to give rise to frequent thrombosis of veins. It gave 75 per cent of improvements, whereas the Mercado mixture, by far the most painful both in its immediate and remote effects, led to improvement in 64 per cent of the cases treated. The chaulmoogra emulsion, while giving rise to very little reaction, only led to 38 per cent of improvements.

Walker and Sweeney believed that chaulmoogra oil contains substances having a high bactericidal activity in vitro. This activity was found to reside in the fatty acids of the chaulmoogric series and to be a function of the carbon ring structure which is peculiar to the chaulmoogric acids. They believed the bactericidal action of these cyclic fatty acids to be specific against the acid-fast groups of bacteria and negative toward all other bacteria. They did not find that other unsaturated fatty acids, which Rogers found therapeutically efficient, possessed the specific bactericidal activity of the chaulmoogric acids. They believed the therapeutic effect of chaulmoogra oil and its derivatives to be due to the bactericidal action of the chaulmoogric acids on B. lepræ.

Marchand has recently made estimations of the cholesterin in the blood of 4 lepers and found it considerably reduced in 3 advanced cases of the disease, being about normal in an early case. In one of the advanced cases it rose considerably after intensive treatment with chaulmoogra oil and the author points out the advisability of further observations on this question in relation to treatment of a larger number of cases.

During the past year Cawston has recommended Oppenheimer's colloidal preparation of antimony which he believes contains sufficient sulphur to counteract any metallic poisoning that might arise from the administration of colloidal antimony alone.

He has reported several cases of leprosy greatly benefited by such treatment. Wildish, at the Leper Asylum Institution in Zululand, has also treated 20 of the worst cases of leprosy with oscol stibium. The majority of the cases received doses of the drug intramuscularly, 2.5 c.c., 3 c.c., and 6 c.c., on consecutive days. Three weeks later 4.5 c.c. and 6 c.c. were given on consecutive days. The series of 2 doses was repeated during the next two months, making a total of about 40 c.c. injected. Beneficial effects were seen in the relief of paralysis, drying of the ulcers, and in the general condition of all the patients treated except one. Equally good results were obtained in a few cases treated with tartar emetic intravenously. Over 1,000 injections have since been given during the past six months. The author after six months believes that antimony is a great help in treating leprosy and possibly is a cure in some cases. It is also useful in combination with ethyl esters and sodium hydnocarpate. Harper reports that the intravenous injection of tartar emetic is useless for leprosy. While a few cases have apparently been benefited by the collodial antimony, a much more extended trial will be necessary before any real efficiency for it can be demonstrated.

Prognosis.—Some observers believe that the disease is self-limited. McCoy says that in the great majority of cases a fatal issue is to be expected within about ten years. However, the duration of the disease may vary from a few months to as long as thirty years, possibly longer. The spontaneous healing of leprosy is recognized especially in nerve leprosy, and a case was recently reported by DeMagalhaes of fifteen years duration, which became stationary, and the patient lived for forty years. The same author also reports 2 cases of tubercular leprosy of twenty and thirty years duration, with healing of the lesions. The disease may sometimes remain for years at a practically stationary condition, the general health of the individual continuing good, and he may be able to pursue his normal vocation. The late Sir William Osler knew well a prominent clergyman who had anesthetic leprosy for more than thirty years, which did not seriously interfere with his usefulness, and not in the slightest with his career. In some cases the life of the individual may be terminated by an intercurrent infection. In a number of instances this may be tuberculosis.

Serum and Vaccine Treatment.—Since the last edition of this work, almost no progress has been made in the question of vaccine and serum treatment in leprosy. Much confusion still exists in regard to the etiological relation which the various microörganisms that have been cultivated from leprosy bear to the disease. The Bacillus lepræ was discovered in 1879 by Hansen in leprous lesions, and following his observations very numerous attempts have been made to cultivate this organism. In the past few years a large number of investigators have described the successful cultivation of various species of bacteria from leprosy, usually believing the one cultivated to be the cause of the disease. These organisms may be divided into five groups as follows, although some of them might perhaps be classified in more than one of these groups:

1. Partially acid-fast or acid-resistant diphtheroid organisms—the Babes-Kedrowsky type. At least 18 investigators have isolated microorganisms which apparently may be included in this group.
2. Acid-fast organisms which produce yellow or orange-colored colonies. Five investigators have probably isolated organisms of this type, Clegg being the first to obtain a definite growth in pure culture.
3. Anaërobic acid-fast organisms isolated by Ducrey, Campana, and Serra.
4. Acid-fast bacilli which do not produce colored colonies. Five investigators, of whom Karlinski was the first, have claimed to obtain organisms of this type. Duval's recent work has been the most convincing regarding the etiological position of this organism.
5. Acid-fast streptothrices isolated by Deycke-Pascha and Reschad-Bey, and Liston.

Wolbach and Honeij (1914), from a very complete review of the literature regarding the various organisms cultivated from leprosy cases, in considering the first four groups mentioned above, believe that there is no way of avoiding very serious attention to the significance of the presence of the diphtheroid group, the pigmented acid-fast group, and the non-pigmented acid-fast group, in connection with the etiology of the disease. The number of times that each culture has been isolated, and the name of the investigator making the isolation may be summarized in the following table compiled largely from Wolbach's and Honeij's article with slight additions:

Diphtheroid organisms: Bordoni-Uffreduzzi, 1; Babes, 12; Spronck, 2; Gianturco, 1; E. Levi, 1; Czaplewski, 1; Teich, 4; F. Levy, 1; Barannikow, 2; Kedrowsky, 3; Klitin, 4; Bayon, 1; Williams, 5; Rost, 7[1]; Shiga, 1; Duval, 1; Ophuls, 1; Wolbach, 1.
Acid-fast pigmented cultures: Rost, 7; Clegg, 16; Duval, 4.
Anaërobic bacilli: Ducrey, 1; Campana, 1; Serra, 3.
Non-pigmented, acid-fast cultures: Weil, 1; Karlinski, 1; Marchoux, 1; Twort, 1; Duval, 8.
Acid-fast streptothrices: Deycke, numerous cases; Liston, 1.

From the collected literature one may conclude that at least two, the diphtheroid and pigmented acid-fast, and perhaps all four varieties of the bacilli have been more or less commonly found in leprosy tissue. The diphtheroid organisms have been found in various parts of the world. In connection with the pigmented acid-fast bacilli, the careful experiments of Clegg and Duval are of particular importance. As Wolbach remarks, the possibility of the partially acid-fast diphtheroids becoming converted into completely acid-fast bacilli must be taken into consideration.

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[1] In Williams' and Rost's cultures it is stated that a non-acid-fast streptothrix gives rise to acid-fast rods, and a non-acid-fast diphtheroid which also produces acid-fast elements.

The employment of various serological tests for the determination as to which type of organism cultivated is the etiological factor in the disease has not led to any very definite results, though it is possible that progress along this line may be made in the future.

Harris and Lanford attempted to identify the various acid-fast organisms isolated by different workers from cases of leprosy by the agglutination test, but they found such a method impracticable. The agglutinin present in the sera of the human subject affected with leprosy they found low in titer and inconstant in action. They were unable to obtain satisfactory sera in rabbits. Positive agglutination tests have been reported with human leprosy serum and the diphtheroid, anaërobic, non-acid-fast, pigmented acid-fast, and non-pigmented, acid-fast bacilli.

Kritschewsky and Bierger, by means of the complement-fixation test, have concluded that Kedrowsky's bacillus is the true bacillus of leprosy, and that Duval's chromogenic culture is not specific for leprosy. With Duval's culture only 2 of the 28 lepra sera they examined gave a strong positive reaction, while with the Kedrowsky culture 24 of the sera gave strong complement-fixation which, however, was less marked in the cases with the nerve lesions of leprosy.

Kraus, Hofer, and Ishiwara have, by the employment of the bacteriolytic reaction, also attempted a differentiation of some of the bacilli cultivated from leprosy lesions. They found that the sera of different guinea pigs which had been inoculated with Duval's and Kedrowsky's organisms developed bacteriolytic properties which could be demonstrated by inoculating the specific serum and corresponding organism into the abdominal cavity of a guinea pig. By this test these two cultures could be differentiated. Duval serum had no effect on Kedrowsky's bacillus, nor Kedrowsky serum on Duval's bacillus. Kraus, however, points out that it is not decided that either organism is the cause of the disease, and he failed to get a reaction with either in human cases of leprosy.

It is necessary to consider particularly in relation to the treatment of leprosy the streptothrix, isolated by Deycke-Pascha and Reschad-Bey, first in 1905, and subsequently by Liston in 1912. Deycke-Pascha and Reschad-Bey by placing leprous material in saline solution and incubating for a long time succeeded in obtaining a growth of an acid-fast organism from a severe case of leprosy. At first the organism was not considered to be Bacillus lepræ. Later it was classified as a streptothrix. From a killed culture of this organism they prepared a vaccine and administered it to a patient from whom they had isolated the organism. A severe reaction followed the injection of the vaccine, and after repeated injections there was an improvement in the patient's condition. Believing that it was probable that the favorable effect noted in this patient was due to immunization with acid-fast constituents of the organism, they turned their attention to the isolation of this acid-fast substance. After many efforts they succeeded by fractional extraction with ether in securing a number of chemical products from the organism. Some of these they rejected as useless, and finally isolated a fatty substance to which the name "nastin" was applied. Nastin, as described, is a true neutral fat obtained from the "Streptothrix leproides" which has been cultivated from different leprous nodules. More recently benzoyl chlorid was added for the purpose of dissolving the bacilli more completely. The new product thus formed was named nastin benzoyl, or nastin B, and it was stated that it did not cause the severe local reactions after injection as nastin alone had done. Nastin has been supplied as nastin B_0, B_1, and B_2. These products are supposed to be of different strength.

Uchida has recently isolated four acid-fast bacilli from rat leprosy cases, one of which produced pigment, while each showed slight differences on culture. Inoculation of rats with cultures did not produce typical rat leprosy though certain lesions were obtained after several months. Which of these four strains if any is the etiological organism of rat leprosy is not yet determined.

Uncertainty of the Successful Cultivation of Bacillus Lepræ.—Notwithstanding the numerous recent observations carried on in relation to the cultivation of Bacillus lepræ, at the present time a number of investigators have not been convinced of the successful cultivation of this organism.

Much work was carried on for several years by different assistants in the writer's laboratory in Manila regarding the cultivation of Bacillus lepræ, and it was pointed out some time ago by him that extreme care should be exercised in regard to the definite conclusion of the cultivation of this organism.

Fraser and Fletcher also incline to the belief that Bacillus lepræ has not yet been cultivated. They made 373 inoculations of the bacilli, obtained from non-ulcerating nodules of 32 lepers, and the tubes were incubated for periods extending to more than six months, but no multiplication was observed except in a few instances where contamination occurred. Blood serum, placental and agar media, Duval's and Williams' modification of Rost's medium were among the media employed, both aërobically and anaërobically.

Diphtheroid bacilli were isolated, but were considered of no importance in reference to etiology on account of their ubiquity. Fraser thinks that the investigators who have described the transformation of a non-acid-fast into an acid-fast organism were deceived by transferring unwittingly lepra bacilli along with other saprophytes.

Bayon believes that Kedrowsky's culture is one of Bacillus lepræ, and identical with the one obtained by himself, but that most of the other organisms which have been cultivated from leprosy lesions are not this organism.

Duval has suggested, upon the ground of serological experiments with immune sera from animals, that neither his non-chromogenic organism, nor the chromogenic one of Clegg is the same as any other known strain of acid-fast bacillus. In one of his most recent publications he believes that comparative biological studies indicate that the Clegg type of leprosy organism is closely related to the moist growing pigment-producing group of acid-fast saprophytes, while the Levi and Kedrowsky cultures, which are apparently the same, correspond in some respects to avian tubercle, and in others to Möller's smegma bacillus. The Rost and Williams culture he believes is identical with Grassburger's acid-fast saprophyte, while Karlinski's culture is not to be distinguished from Rabinowitsch's butter bacillus. He believes that Bacillus lepræ has been cultivated by himself, and that there can be no doubt that the non-chromogenic acid-fast strain is the true leprosy bacillus, and states that the non-acid-fast streptothricial and filamentous forms which have been described as "stages" of Bacillus lepræ by Kedrowsky and others have not been noted in any culture which he has isolated. He believes the organism of human leprosy is a bacillus and not a streptothrix. It must be admitted that at the present time there appears to be no unanimity of opinion as to which culture, if any, is one of the true etiological factors in leprosy.

Since there still exists so much confusion in regard to the etiological relationship of the various cultures isolated from leprosy cases, as might be expected, the favorable results obtained in treatment with various sera and vaccines obtained from these cultures are not very obvious. Therefore, in a consideration of the subject at the present time, it is perhaps more advisable merely to review the results which have been reported by the different investigators with the various sera and vaccines employed.

Serum Treatment.—In 1896 and 1897 Carrasquilla reported upon the successful treatment of lepers by means of a serum which he had prepared in the following manner: Blood was drawn from young lepers, allowed to coagulate, and the serum pipetted off. At intervals, from 50 to 100 c.c. of this serum was injected into horses, the animal being later bled, the serum collected and used for treatment. In the first report it was stated that 15 lepers had been cured by use of the serum. A number of investigators, Buzzi, Barillon, Alvarez, Arning, Atherstone and Black, Dehio, Grunfeld, Tidswell, Thompson, Medina, and Putnam, have employed Carrasquilla's serum in the treatment of leprosy. While temporary improvement has been noted in some instances, after its use the consensus of opinion at the present time is that this serum is of no value in the treatment of the disease. Babes in 1893 immunized animals with avian tubercle bacilli and injected the serum from such animals into lepers. In 1899 he prepared an extract from an organism isolated by him from leprosy cases, inoculated this organism into animals, and also employed their sera for treatment in human cases of the disease. No definitely favorable results have been obtained by this method of treatment. Abraham and Herman excised leprous nodules and subjected them to pressure, thereby expressing the fluid contents and lepra bacilli, diluted this fluid with normal saline solution, and injected it subcutaneously into horses, several cubic centimeters being inoculated every week or two for a period of four and one-half months. Four weeks after the ninth injection the horse was bled, and the serum collected and used for the treatment of several cases of leprosy. With one exception no favorable results were noted.

Laverde obtained leprous nodules and used the tissue fluids from them to inoculate goats and donkeys. Patients were treated with the serum from these animals and the author states that marked improvement occurred in the leprous lesions, and a disappearance of anesthesia was noted. He continued the treatment for periods varying from three months to a year, and continued to produce improvement in 60 patients. Six of these cases, he stated, had been cured by this treatment. Further reports of its use have not been forthcoming.

Sugai, Mabuchi, Mononobe, and Ohashi obtained serum by inoculating goats with suspensions made from leprosy nodules. Only indefinite results were obtained by treatment of cases with this serum.

Metchnikoff showed that a serum produced by the methods of Carrasquilla and Laverde was cytotoxic rather than antitoxic or bactericidal in its action, and that analogous effects are produced by the serum of a goat inoculated with normal human blood.

In 1912 Currie, Clegg, and Hollmann prepared a serum in horses by injecting at short intervals live cultures of acid-fast bacilli suspended in normal saline solution. The cultures had been isolated from lepers. Injections were given into the jugular vein in increasing doses, until finally 18 to 20 agar cultures were given at a dose. After the injections the animal became ill, and its temperature sometimes rose to 40° C. After several months of treatment of this kind the animal was bled, and it was found that its blood serum clumped the organism they had isolated from leprosy cases in dilution of 1:1,000, and strongly in a dilution of 1:500. No clumping occurred with Bacillus margarin, Bacillus smegmæ, or the grass bacillus of Möller. The serum appeared to exert an inhibiting effect upon the growth of the organism with which it was prepared. The authors found that injections of this serum into patients suffering from leprosy did not, during the short period of time in which they used it, produce any beneficial results. They are not, however, without hope of increasing the potency of this serum to a point where it may be of benefit in the treatment of the disease.

Janin (1913) applied blistering fluid or plaster to portions of the skin of lepers in which the nodules were numerous, and injected 8 to

10 c.c. of the serum resulting into the same or other patients. The first case treated was one of nodular leprosy of five years' standing. After 6 injections of the patient's own serum given at intervals of ten days the lepromata disappeared and the skin regained its normal appearance. A second leper who had been suffering from the anesthetic form of the disease for four years was benefited by 3 injections of the serum of the first case. A subject of macular leprosy who was in feeble health improved considerably after 6 doses of his own serum obtained by blister. Another similar case received 4 injections after which the eruption grew paler and sensibility was restored in the more recent patches. Four injections of this man's serum were given to a girl who had been an anesthetic leper for four years. No change was noted in the lesions, but her health improved rapidly. Four doses of the same serum were administered to a man suffering from anesthetic leprosy of ten years duration and who had perforating ulcer of the foot. The ulcer healed and the patient became stronger, but the leprous areas of the skin remained unaltered. The author concludes that the blister exudate of lepers exerts a specific effect upon the course of the disease. A sharp febrile reaction sometimes occurs after the first injection.

Paldrock, in the treatment of 4 cases of leprosy, employed fresh complement-containing serum from animals together with arsphenamin. He was led to make this experiment on the ground that the serum of lepers might be deficient in complement which has, however, been shown not to be the case. Increasing doses from about 35 c.c. to over 100 c.c. were given subcutaneously, each patient receiving in all from 285 to 325 c.c. of serum. No benefit appears to have resulted from this method of treatment.

Dyer, influenced by the report of the condition resulting from the accidental biting of a leper by a viper in the West Indies, used the antivenom serum of Calmette in a series of leprosy patients with almost uniformly good results. Three of the patients recovered. Injections were made at frequent intervals, sometimes daily, and the dosage varied from 5 to 20 c.c. The buttocks and the shoulders were the usual sites of injection, though frequent injections were made in the lesions themselves, with the interesting result that these were directly influenced to favorable resolution.

Woodson has reported upon the same treatment with one case of leprosy which showed improvement, but the author doubted whether this was due to the serum alone.

Vaccine Treatment.—Scholtz and Klingmuller recommended the tissue juice expressed from lepromata for the treatment of leprosy. Castellani and Woolley also employed a similar method of treatment. Woolley excised a nodule from the arm of a leper, ground it with sand in salt solution, centrifugalized, heated to 65° to 70° C. for fifteen minutes, and added enough carbolic acid to 5 per cent. The suspension was rich in bacilli. At intervals subcutaneous inoculations of .01 c.c. were made. Woolley later reported that no success had been obtained with this method.

Nicholls (1908) removed a leprous nodule together with a quantity of surrounding tissue. This was placed in a tube of glycerin bouillon and incubated for a fortnight. The broth and tissue were then slowly desiccated. The dried mass was finally powdered in an agate mortar, a suspension made, and the bacilli killed by heating to 60° C. and counted in a blood-counting apparatus. It was believed that during the time of incubation of the tissue the bacilli had multiplied therein. A case was treated with this substance which was said to contain 50,000,000 organisms per cubic centimeter. Under this method of treatment given every four days at first and later every seven to ten days, some nodules disappeared and others softened.

Rost in 1905 and 1909 prepared a substance known as leprolin from an organism which he stated had been cultivated from a case of leprosy. In a later report (1912) his method of preparation of the vaccine is as follows: Bacteria were removed from an agar slant culture of the organism, shaken up with distilled water, and centrifugalized, the fluid being poured off and fresh distilled water added to the deposit, shaken up again, and again centrifugalized several times so as to wash the culture and remove all external toxins. The deposit of bacteria, after final washing and centrifugalizing, was dried and weighed and macerated with 7 per cent glycerin and distilled water to make up a percentage solution. It was then placed in tubes and autoclaved. The tubes were then sealed and placed on a shaking machine for a period extending over several weeks. Ten minims of 1 in 400 of this vaccine produced a slight febrile reaction in cases of leprosy, and its therapeutic usefulness, according to the author, was very marked. Later another method of preparation of a vaccine was sometimes employed, the fatty substance of the bacteria being extracted by shaking in ether over a period of several weeks, filtering and centrifugalizing the deposit, and evaporating the ether extract until it became of a sticky consistence and then adding olive oil to a weighed amount. Finally he prepared leprolin from six-weeks-old bouillon cultures by filtering through paper and then sterilizing. One to 3 c.c. are injected into the muscles every week. Of 30 lepers treated with his leprolin since 1909, 4 are said to have been cured and improvement has been noted in many others.

Whitmore and Clegg prepared a vaccine with the organism previously isolated by Clegg. The culture was killed by heating and suspended, and an attempt made to standardize it to 500,000 bacteria per cubic centimeter. The bacteria in this vaccine showed a great tendency to form clumps, on being allowed to stand without shaking. Injections were given once a week in doses varying from 0.25 to 1 c.c. of this substance. Any increase above this dose produced a local reaction preventing the absorption of the bacilli, and later an abscess would form at the site of the injection. Eleven cases of leprosy were treated in this manner for eight months, and 21 cases for seven months. None of these cases showed any improvement and the abscess production was considered a serious obstacle to the treatment. They next employed a glycerin extract from the organism isolated by Clegg, made in a similar manner to tuberculin. This substance gave no reaction in lepers analogous to von Pirquet's skin reaction in tuberculosis. Thirty-two cases of leprosy which had been previously treated with the first vaccine then received this substance. No reaction followed this treatment, and there was no improvement at the end of two months. They then made a preparation by emulsifying cultures of this same organism in 1:60 aqueous solution of sodium oleate, the bacteria being almost completely dissolved by this fluid. In 2 cases which were treated for two and one-half months with this substance, no improvement resulted. The spleen of a leper which was rich in leprosy bacilli was ground up and the substance suspended in a 1:60 aqueous solution of sodium oleate filtered through cotton and heated for one hour at 60° C. None of the patients treated with this substance showed any improvement.

In 1912 Currie, Clegg, and Hollmann continued attempts of specific therapy in leprosy, using in addition to serum the following preparations for treatment: (1) a vaccine prepared by practically the same method as previously described by Clegg and Whitmore; (2) the injection of living cultures suspended in saline solution, inoculations of 1 c.c. being given at a dose; (3) inoculations of lepra toxin prepared from cultures of the leprosy bacillus after the method used by Koch in preparing the different tuberculins; (4) extraction of fatty substances from the cultures by chloroform and alcohol, prepared somewhat in a similar manner to nastin; (5) a few experiments made with sensitized killed cultures, that is, cultures which had been exposed to the serum of monkeys previously injected with their leprosy cultures.

They conclude that: (1) Vaccine made in the ordinary way and administered subcutaneously cannot be employed advantageously except in very small doses, since any attempt to give large quantities results in abscess formation locally, and a very slow absorption. (2) While live cultures of Bacillus lepræ have produced no beneficial results, they are deserving of further trial. They also produced abscesses unless given in small doses. (3) Toxins prepared from Bacillus lepræ after the method of Koch's old tuberculin and his "B. E." appear to be of slight or no value in the treatment of leprosy. The extract consisting of the fatty material obtained from their leprosy cultures was not employed for a sufficient length of time to determine whether it was of value in the treatment of leprosy.

Williams, who regards his organism as identical with Rost's, as has been mentioned, cultivated a streptothrix from leprosy lesions and also prepared a vaccine, first by suspending the organism in olive oil or in salt solution after drying and powdering in a mortar. Later a six-weeks-old bouillon culture of the organism (presumably in which the organisms were killed) was employed. This vaccine was used upon lepers accompanied by improvement in some of the cases.

Sandes, during 1912, treated 8 cases of leprosy by a suspension of killed "leprosy bacilli." The description of the culture is not given. At first 10,000,000 of the killed organisms were injected, and later the concentration of the bacilli was doubled, trebled, and quadrupled. No favorable results were obtained.

Turkhud, in 1913, prepared leprosy vaccine in the Bombay Bacteriological Laboratory from this same streptothrix isolated by Williams, and distributed to various physicians the vaccine for the treatment of leprosy cases. Fifty-nine cases of the disease were treated in various parts of the world, improvement being reported in 21 cases. The results vary with the observer.

Watkins-Pitchford noted no beneficial effect in 10 cases. Turkhud himself states that improvement in some cases in his experience is very definite, although marked and speedy improvement in every case has by no means occurred. He states the injections must be repeated every ten days for months. Sometimes a severe reaction results.

Rutherford treated 32 cases of leprosy occurring in natives of India with a vaccine prepared from Williams' culture. Ten of these patients disappeared during the period of treatment. Of the remaining ones the shortest period of treatment was one hundred days, and 15 were treated for one hundred fifty-three days. Two cases remained unaltered in condition. In 3 cases it was impossible to decide whether there had been on the whole improvement or deterioration, and the remaining 15 cases grew worse. The author considers that the deterioration in these cases was probably usually due to the natural progress of the disease, and that the treatment did not affect it one way or the other. The vaccine was given usually in doses of 1 c.c. injected weekly.

Davies, 1913, has reported upon the treatment of a case of leprosy in a European girl, aged eight, with injections of an extract made from Bayon's bacillus. The maculæ became red and inflamed a few hours after the injections, but soon improved. Six months later those on the body and limbs were almost invisible, but those on the face persisted, although they had faded to a great extent. The remedy was tried on 6 other lepers, but the results are not reported.

Bayon has treated 126 cases of leprosy by injections of a filtered diluted extract made from Kedrowsky's culture. He considers that the employment of a simple vaccine made of the bacilli killed, but not otherwise treated, can be of no service in this disease, since such organisms are not broken up in the tissues and no antibody formation can result. The extract from Kedrowsky's culture produces in early cases of the disease an intradermal reaction which may be used to confirm the diagnosis. The ultimate result of the treatment of the cases is not known.

Heiser has also reported in 1913 the cure of 2 lepers, both of whom had received vaccine treatment, but who appeared to be equally or more benefited by the other medical treatment which they had received.

Treatment with Nastin.—In regard to the treatment with nastin, many observers feel that the treatment is of no value, while others report in its favor. Among those observers who have obtained no favorable result may be mentioned Brinkerhoff and Wayson, Engel-Bey, Feindel, Jeanselme, Kinoshita, Kitasato, Lenz, MacLeod, Gordon, Messum, Montoya and Florez, Neish, Petrini, Peiper, Rogers, Sadikoff, Sakagachi, Ashburton Thompson, Teague and Whitmore and Clegg. The results obtained by Anderson, Biehler, Neil Campbell, Chatterjee, Davidson, Gottheil, Jackson, Kiwull, Krikliwy, Kühne, Kupfer, Lie, Raschid, Rodriguez, Smith and Bisset, Williams, Wise, Ziemann, while not entirely conclusive, on the whole seem to show that the remedy probably seems to influence the disease favorably. Only some of the more recently published results will be considered in this article.

Minett has treated 18 selected cases with nastin for nearly two years, and 6 for six to nine months, before further treatment with benzoyl chlorid was begun. These cases were compared with 71 unselected, treated only with benzoyl chlorid, and with 8 other cases left untreated. Each group included cases of nodular, anesthetic, and mixed leprosy. The author finds that with nastin alone very little beneficial effect was produced.

Schumacher has employed nastin in the treatment of 4 natives of German East Africa, all of whom suffered from mild skin lesions of leprosy of long standing. All 4 received subcutaneous injections, weekly at first, of nastin B_1 for eight weeks, and then after fourteen days interval of nastin B_2 for sixteen weeks. No general reaction was observed at any time and no reaction at the site of the injection. A favorable change occurred in the lesions of the skin and in the nasal lesions. Two months after the last injection the spots could be recognized only by small nodules which had become dark and softer. Lepra bacilli could no longer be found in the nasal discharge. Unfortunately the observation of the cases could not be continued longer.

Rudolph reports 6 cases of leprosy treated with nastin in which improvement occurred in all but one. In the last case treated the patient had been afflicted for five years, and incapacitated for two years, suffering from a mixed form of the infection complicated with iritis. In a course of eighteen months he received 3 injections of nastin B_0, 8 of nastin B_1, and 12 of nastin B_2. After six months treatment the iritis disappeared and the anesthesia was less. The lepromata on the hands and forearms became softer, but leprosy bacilli were still present. At the end of eighteen months he had much improved. Bacillus lepræ was not discovered in the nasal secretion. The photographs taken before and after treatment afford convincing evidence of the improvement which took place.

Peiper records observations upon 31 lepers treated with nastin since the year 1907. Three are believed to have recovered, and 6 to have much improved under this treatment.

Dr. Verteuil reports that in 2 anesthetic lepers an arrest of the disease occurred after 38 and 67 injections of nastin. In order to be successful the author states the treatment must be continued for two or more years. He believes nastin is contra-indicated in ulcerating leprosy.

Wise and Minett, during a period of four years, treated by injections of nastin 244 unselected patients in British Guiana suffering from leprosy in various stages. Of this number at least 206 were under treatment for more than one year, and 118 for more than two years. Treatment was begun under the personal supervision of Deycke, who stayed some months in the colony, and afterwards the treatment was continued on the general lines laid down by him. The results obtained by the authors are not very encouraging. Some degree of improvement, they feel, is undoubted during the three to six months, but this early improvement is a slight one and only temporary. The condition retrogresses, the patient relapses, and the disease goes on as before. The experience in British Guiana shows that during the first six months of treatment there is a slight temporary check of the disease, but otherwise the natural course continues unchanged.

Scott analyzes the results in 49 cases treated by nastin, continued for considerable periods. Only nastin B_1 was used and a full tube was injected at each dose. The injections were given intramuscularly in the intrascapular region, the skin being sterilized with iodin. The results in the treatment are shown in the table on page 710.

In the opinion of the author the improvement noted in 85 per cent of the cases constitutes sufficient ground for a very favorable conclusion. He remarks that the good effects are not strikingly rapid. They are slowly and gradually developed, and are often not easily observed. They are nevertheless found to be substantial when treatment is sufficiently prolonged, and a careful estimate made of its results.

Non-specific Vaccine Treatment.—Many observers have also attempted to employ tuberculin in the treatment of leprosy. Since such a method of treatment is obviously not specific for leprosy it will not be considered in detail, but in general it may be stated that while improvement has occasionally occurred in some, no definite improvement has been obtained in the majority of cases. In a number of instances such

Results of Treatment by Nastin

Length of Time under Treatment	"Cured"*	Greatly Improved	Considerably Improved	Somewhat Improved	Stationary	Worse
3 years and over..........	1	..	..	..	..	..
2½ years and over........	..	1	..	..	..	..
2 years and over..........	..	2	..	..	..	1
1½ years and over........	1	1	1	..	..	..
1 year and over...........	4	3	3	5	1	2 †
9 months and over........	..	4	4	3	..	1
6 months and over........	1	1	2	1	..	..
Under 6 months..........	1	..	2	1	1	1
Total.............49	8	12	12	10	2	5

* "Cured" means complete restoration to health, strength, and working power, with loss of every symptom which causes inconvenience or incapacity. It does not mean in every case complete disappearance of every sign of leprosy.

† Intercurrent dysentery. Leprous symptoms had improved.

treatment has been reported apparently to have been injurious to the patient.

A few investigators have also employed in the treatment of leprosy vaccines made from streptococci isolated from cases of erysipelas and one observer from yeast cells, but no beneficial effect was noted in the cases so treated.

Spontaneous Cure and Improvement in Relation to Treatment.—Numerous references are found in the literature to spontaneous recovery among lepers and to cures by various forms of drug treatment. Some observers have believed that the disease is self-limited. It should therefore be borne in mind that, in the treatment of leprosy by the various vaccines and sera considered above, errors in judgment are particularly liable to occur, and undoubtedly have occurred in many of the reports which have been referred to in this article. The irregular course which the disease pursues, sometimes with periods of temporary improvement and at others of retrogression, further increases the difficulty of determining even after an extended trial the value of a therapeutic agent.

Vaccination against Small-pox of Lepers.—In earlier years it was believed in Hawaii by the natives that vaccination might be the cause or at least the exciting cause of leprosy. Denney and Hopkins have recently reported that vaccination (employed as a prophylactic measure) against smallpox of 118 lepers at the National Leprosarium, Carville, Louisiana, showed that the vaccinia in the lepers ran an abnormally violent course, evidenced in the majority of cases by excessive local inflammation, necrosis, and ulceration, and accompanied by unusually high fever and even severe prostration. Appearing coincidentally with the symptoms of severe vaccinia and even in some cases of unsuccessful vaccination were other manifestations specifically leprous in character, definite leprous lesions appearing in a number of cases which might be attributed to the effect of the vaccine. Some of the leprous lesions developed not only near the site of the vaccination, but were generally distributed over the entire body. Nerve disturbances were also observed in the nerve type of the disease. No case, however, was permanently aggravated by the smallpox vaccination and some showed actual amélioration. Denney concludes that a symbiotic relation existing between vaccine virus and the bacillus of leprosy offers the best explanation of the phenomena observed.

Hasseltine at the leprosy investigation station in Hawaii has also reported similar results after the vaccination of 27 lepers. In the cases unsuccessfully vaccinated, however, no evidence of any change in the leprous lesions was noted, but, of the 19 successfully vaccinated cases, 11 developed acute leprous eruptions in the two weeks following the date of vaccination. At the date of writing, one month after vaccination, all the cases that showed eruption had returned to normal except for some desquamation at the former site of the eruption.

PROPHYLAXIS

Etiology.—In discussing the prophylaxis of leprosy it is important to refer to certain etiological factors regarding the disease, and particularly to its method of transmission. The problem is complicated by the fact that we are still in ignorance of the exact method by which leprosy is acquired or transmitted from the patient to the healthy individual, although it is generally believed that leprosy is communicable and that in some manner the bacilli pass from the sick to the well, and that in at least a small proportion of such instances the disease is reproduced.

The influence of climate upon the spread of leprosy is not clear. While leprosy is generally classified as a tropical disease, and more commonly occurs in tropical countries, this is probably largely due to the state of civilization and the insanitary conditions which prevail in such countries. The disease, as is well known, was formerly very common in Europe and is still common in Iceland, which would appear to demonstrate that climate is not alone at least a determining factor in its distribution and spread. Whether race itself predisposes to the disease also seems doubtful. While leprosy occurs more frequently in Orientals, Polynesians, and Africans of the poorer classes, the conditions under which these people live undoubtedly expose them more frequently to infection, since uncleanliness and overcrowding favor its transmission. The disease has its onset particularly in youth and early adult life. Cases are rare in very young children and the disease is also uncommon after seventy years; in fact, the majority of the cases occur between the tenth and thirty-fifth year. The number of males attacked with leprosy is almost double that of the females, but apparently there is no satisfactory explanation of this fact. During the course of the disease the fertility of the female does not appear to be impaired, but the fertility of the male is materially reduced, often by the existence of leprous orchitis. Noel has recently shown that menstruation is not modified by leprous infection, that it usually appears regularly, and continues in a normal manner until the menopause. From certain statistics at Molokai it appears that the birth-rate of lepers is probably two-thirds as high as that of the non-leprous members of the same race. When, however, the father is a leper, the birth-rate is only about one-third of that when the mother is a leper.

Portal of Entry of the Organism.—Stricker advanced the idea that the initial lesion of leprosy was to be found in the nasal mucous membrane and in ulcerations of the nasal septum, and that it was by the atrium of the nasal mucous membrane that infection occurred. Nasal lesions are certainly common and early in leprosy, and the Bacillus lepræ is often found in the nasal mucous membrane and in the discharges from the nose, so often that bactericidal examination of these discharges is a valuable aid in diagnosis. However, it is the consensus of opinion to-day that there is generally no recognizable primary lesion in leprosy, and that while the leprosy bacilli are frequently passed into the surrounding atmosphere of lepers by sneezing and coughing, for example, the evidence that man acquires the disease in this manner, or by kissing, is not convincing. However, it should be borne in mind that this may represent one channel of infection. The same may be said regarding the occurrence of infection by inhalation of dust containing the leprosy bacilli. Many observers believe that the common mode of infection of leprosy is, in all probability, through accidental abrasions or other lesions of the skin.

Occurrence of the Organism.—In those afflicted with the disease the leprosy bacillus is generally present in the granulomatous lesions in very large numbers, in the lymph spaces as well as within cells called "lepra cells," and in endothelial and connective tissue cells. The organism may be found in almost any part of the body in different cases, with the exception of the muscles, bones, cartilages, and intestinal tract. It is very abundant in fluid expressed from the nodular leprous lesions, in the ulcerations of the skin, and is often found in the sputum as well as in the nasal mucus. It is usually not found in anesthetic areas of the skin. In such cases the bacilli are located in the nerves which supply those areas lying between the fibers and within the nerve cells. The bacillus is also found in the enlarged lymphatic glands. In the internal organs it is particularly prevalent in the liver and spleen, lying both free and within the cells. The organism has also been found in the circulating blood, particularly during the febrile periods. Hence it is evident that large numbers of leprosy bacilli are continually being given off from the leper patient, particularly through the secretions and open lesions, and in fact these bacilli are often found in the immediate surroundings of lepers. However, it is questionable whether many of these organisms are alive or at any rate sufficiently virulent to infect the healthy individual. While the percentage of attendants and physicians administering to lepers who become infected is small, nevertheless such infections do occasionally occur. The very long incubation period of the disease which, it is believed, may vary between one and ten years obviously renders more difficult the detection of the method of infection in any given case.

Evidence of Transmission by Inoculation.—Numerous attempts have been made to inoculate man experimentally with leprosy by the subcutaneous injection of leprous material or with supposed cultures of the leprosy organism. These have all resulted negatively except in one doubtful instance in the case of a convict who was inoculated with an excised leprous nodule inserted under the skin and who developed lesions of the disease after three years. However, several members of his family had in the meantime contracted leprosy in a natural way. The lesions in the case of this convict developed first at the site of the inoculation. McCoy, who considered very fully the data available on the case, thought it highly probable that this convict was actually infected artificially with leprosy. On the other hand, Danielson inoculated himself and 9 others, as did Profeta, with material from the lesions of nodular leprosy, but failed to produce the disease. Accidental inoculation of physicians or attendants upon lepers with leprous material on surgical instruments through cuts or abrasions of the skin have also generally resulted negatively. However, Rogers has reported 2 cases of doctors who wounded their fingers while operating on leprous patients and both not long after developed leprosy commencing with anesthesia in one and red leprous patches in the other on the very fingers they had wounded. There seems little doubt that the susceptibility to the disease, just as to tuberculosis, must vary very greatly, and it would appear that many healthy individuals are at least relatively immune to leprosy.

Attempts to infect animals successfully with the disease are quite unconvincing, although a large amount of experimental work has been performed on this subject. Inoculations into the eye of rabbits appear to have given results that are more nearly successful of an infection than in others, but these experiments are still not sufficiently convincing. In connection with the subject of the inoculation of animals with leprosy, the leprouslike disease which occurs spontaneously in rats, and was first described by Stefansky, is of interest. Two types of the infection are encountered: one in which the skin and muscles are involved, and the other the lymphatic glands. Dean showed that this disease of the rat has a remarkable resemblance in its pathological, anatomical, and bacteriological features to leprosy in human beings. Agglutination of the organism of rat leprosy was said to occur with the serum from human cases of leprosy. While it seems that the two diseases may be closely related, human and rat leprosy are probably not identical. The distribution of rat leprosy does not accord with that of human leprosy, and McCoy reports that it appears to be absent in such a well-established focus of the human disease as Hawaii.

Insect Transmission.—It has been claimed that leprosy may be transmitted by flies, bedbugs, fleas, ticks, lice, itch mites or chiggers. Particularly during the febrile periods of leprosy the Bacillus lepræ may circulate in considerable numbers in the blood, and any blood-sucking insect might ingest this organism. Thus Rudolph has found the leprosy bacillus in the intestines of a tick Amblyomma cajennense, which had sucked blood from a patient suffering from nodular leprosy, for as long a period as thirteen days. Valverde has recently pointed out that there is a marked lack of experimental support in the evidence presented by Lutz that the mosquito is the transmitting agent in leprosy, while Marchoux has shown that, at least in the case of rat leprosy, flies can only transmit the disease in the immediate neighborhood on their feet, as the bacilli are quickly dried and rendered inert, and also that the bacilli will not live in the intestine of the fly. Borrel, Majocchi, and Serra have recently called attention to the possible rôle of Demodex folliculorum as a cause of leprosy. Majocchi reported the existence of Demodex and leprosy bacilli in 8 out of 11 cases of leprosy in which comedones were examined, and Serra found in 17 cases of nodular leprosy Demodex together with leprosy bacilli in 8. The parasite and bacilli were also present in 5 of 16 mixed cases, and in 2 of 25 anesthetic cases. Thus, in relation to the transmission of the disease by this parasite as well as with the other inserts mentioned, it may be said that the evidence is not convincing, though in some instances it seems possible that transmission might sometimes be accomplished by some of these insects. It must be borne in mind, however, that leprosy may be transmitted in more than one way and possibly in several ways.

With reference to Hutchinson's theory that the disease bears relation to the eating of fish or of salted or spoiled fish, or that individuals are more predisposed to the disease through such diet, we can only say that this theory has received no important support in recent years, nor has there been important evidence submitted which points to the acquiring of the disease through the alimentary tract. Innutritious food and lack of suitable food, however, just as unhygienic and insanitary surroundings, must be admitted as among the chief predisposing causes of leprosy.

Vaccination.—It has been claimed that vaccination against smallpox has been a means of spreading leprosy. While this might be a possibility, if human lymph infected with leprous material were employed, obviously when bovine lymph is used there could not even be a chance of occasional infection. However, as is called attention to elsewhere in this article, vaccination not infrequently causes the development of fresh leprous lesions in lepers.

Contact Infection.—Although the exact method of transmission of the disease is not known, most authorities agree that every case of leprosy owes its origin to contact direct or indirect with some other individual suffering with the disease, and by close association with lepers one would appear to be undoubtedly exposed to danger of infection. The often quoted case of Dr. Hawkley Benson would appear to demonstrate the danger of contact and close association. In this instance a leper who developed the disease in the West Indies returned to Iceland where he subsequently died of the disease. His brother, who had never been in a country in which leprosy prevailed, but who lived with him and often wore his clothes and occupied the same bed, developed the typical disease after about five years. In countries where leprosy prevails, it is not uncommon to find several lepers in one family, and sometimes the cases develop one after the other. Denney, in the statistical analysis of 10,400 cases in the Philippine Islands, found that 29 per cent of the patients gave a definite history of previous contact with at least one leper relative. McCoy has reported that, in addition to the famous case of Father Damien, 2 white attendants, both Europeans, have developed the disease at the Molokai Settlement, and other examples of such contact infection could be cited from leper institutions situated elsewhere. It is a remarkable fact that even when contact would appear to give the most favorable opportunity for infection between the diseased and the healthy, as often occurs in leper colonies, that the disease is rarely contracted, and even between infected husbands and wives not over 5 per cent of adults contract the disease.

There is a firm conviction in the minds of many observers that leprosy is spread by sexual intercourse, and this method of transmission cannot be denied, though obviously it is not the only method of spread, since the disease is often observed in young children. Jeanselme found leprous urethritis and numerous bacilli in pus from the meatus, and believes that the disease may be undoubtedly transmitted by sexual intercourse. In the Hawaii Leper Colony it was found that of 98 healthy residents who lived with diseased wives, only 5 developed the disease (4.9 per cent), and of 83 healthy wives who lived with diseased husbands, only 4 developed the disease (3.3 per cent). On the other hand, the children of leprous parents frequently develop the disease. Kitasato's statistics show that 7 per cent of the children of lepers become infected. Denney found that no less than 44 per cent of the children living with leper parents contracted the disease, and Lie, in Norway, among 481 marriages of lepers, found infection in no less than 39 per cent when both parents were lepers.

Heredity.—In spite of the fact that leprosy bacilli have sometimes been found in the placenta, foetus, and milk of leprous women, we know that children of leprous parents are generally born healthy. Zambaco states that he has seen congenital cases of leprosy, and Nakayo has reported a case in Japan of a newborn infant with typical leprous infiltrations and bacilli. These are very unusual exceptions. McCoy, while admitting that the children of leprous parents develop the disease much oftener than the children of healthy parents among the same population, points out that the children born in leper families are not likely to develop the disease if removed at once from the leprous surroundings. In a report of the Nasik Leper Asylum, of 44 children which were removed to a home situated over two miles from the asylum, 34 later passed out uninfected; 8 later became married and their children are perfectly healthy, as are also the 10 which remained at the home, at the time of the report. At the Ramchandrapuram Asylum, of 40 children born, only 3 contracted the disease, 2 of which had long lived with their leprous fathers before being admitted to the home. It is therefore evident that there is not the same tendency for the children to contract the disease from their parents if they are separated from them shortly after birth.

It would appear, therefore, that the one prophylactic measure of value that we know of in leprosy is the prevention of exposure of healthy persons to lepers, and this can obviously best be accomplished by the detection and segregation of those afflicted. The prevention of the exposure of children and young adults to lepers would also appear to be particularly important in controlling the disease. It also is obviously advisable to separate husband and wife as far as possible when either is a leper, and it is even more advisable to separate them when the wife is a leper, as the chance of childbirth is three times greater.

It should be borne in mind, however, that in nerve leprosy, where there are no leprosy bacilli in the nasal discharge or in the sputum, the chance of infecting others is comparatively small. Nevertheless, in cases of nerve leprosy the mucous membranes of about 25 per cent have been shown to contain leprosy bacilli. Where a leper is not excreting bacilli, or where acid-fast organisms cannot be found after careful search, he would appear to be no particular danger to the community, but such patients should be kept under close observation and frequent bacteriological examination should be performed. Individuals with extensive and ulcerating lesions of the skin should certainly not be allowed at large.

Some authorities question the value of segregation, and recently Albert has shown that segregation and isolation of the cases in the Philippine Islands has been of very doubtful efficacy since, in the past seventeen years, the annual crop of lepers has shown no marked diminution. Also in Hawaii segregation and isolation does not seem to have had any very marked influence on the spread of leprosy among the native Hawaiians.

However, we cannot deny that the greater the number of lepers moving freely in a communuity, the greater is the likelihood of the other members of the community who associate with them becoming infected with the disease; and McCoy, who formerly did not regard the results at Hawaii as very successful, more recently points out that, if a country in three or four generations brings the scourge under control in the sense not that it has actually been exterminated but that cases have become vastly less numerous than they were, any efforts in this direction may be regarded as well justified. He believes that, in the efforts both at Hawaii and Scandinavia, we have evidence that persistence in separating the lepers from the general mass of the population will result in the gradual decline of the disease and perhaps result in extinction. Of course attempts at thorough and complete isolation of lepers often defeat their purpose since the coöperation of lepers and their friends may not be obtained and the patients with leprosy are often concealed from the authorities. However, much can be accomplished by general education of the public regarding the disease and the danger of contagion. Dyer says as soon as compulsory confinement is required by state law the leper seeks and usually finds concealment, and the condition is thus made worse. If, however, the state makes provision for adequate treatment under proper surroundings, these patients will usually seek relief. Such persons who cannot be made by the laws of the country or persuaded to enter institutions devoted to the care of lepers should be isolated as much as possible from the public and the members of their family. When lepers live in their own homes they should occupy a separate room or preferably a separate cottage. Their clothing, bedding, personal articles, and eating utensils should be kept strictly apart from those of other members of the family and their laundry should be done separately. Their discharges, surgical dressings of any lesions, and underclothing should either be carefully sterilized or destroyed. In connection with prevention, it should be borne in mind that early detection and diagnosis of the disease is very important, and, in communities where leprosy prevails, physicians should be given special instructions in regard to its diagnosis. When a case is detected it should be treated as at least one of a feebly contagious nature, and in connection with its spread it must be borne in mind that there is no reason to suppose that infection takes place through only one channel.

With reference to disinfection, many authorities consider the free use of soap and water the most important means of avoiding the infection. Rooms or buildings formerly occupied by lepers, and which are to be used for the dwelling of others, should first be fumigated in order to destroy any insects present which may possibly assume a rôle in the occasional transmission of the disease. Later there should be a general disinfection of the room or house with bichlorid solution, 1:1,000, or carbolic acid, 1:30, and all personal belongings, dishes, etc., should be disinfected either with one of these solutions or in boiling water.

Diagnosis.—A correct diagnosis of leprosy is often of much more importance than is the case with most diseases, since it usually involves the whole future of the patient. On the other hand, failure to diagnose a case may permit the exposure of many healthy individuals to infection. Therefore the greatest care must be exercised in making a diagnosis of this disease. Both the lesions present and the bacteriological study must be carefully considered. Even if acid-fast bacilli are found in smears of the nasal mucous membrane, in the absence of definite clinical features, great caution must be exercised, since acid-fast bacilli have occasionally been encountered in healthy individuals. Stitt and Climenko have emphasized the difficulties in distinguishing Morvan's disease (syringomyelia) from leprosy. For the diagnosis of the disease the reader must consult authoritative articles upon this subject, since it cannot be considered in detail in this article.

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INFECTIONS DUE TO VIBRIOS

CHAPTER XXVII

ASIATIC CHOLERA

RICHARD P. STRONG

Although the specific organism of Asiatic cholera was discovered forty years ago, and much has been accomplished in the prevention of epidemics of this disease in many parts of the world, it nevertheless still continues to be a widely prevalent and dangerous infection in certain countries. Thus, for example, in India, where during the past twenty years there have been approximately 8,000,000 deaths from cholera, the mortality from this disease has averaged between 300,000 and 400,000 per year. Epidemics of cholera in more sanitary and civilized countries often originate and spread quickly and without warning. One need only recall the epidemic in Hamburg in 1892 in which within two months time there were nearly 17,000 cases and over 8,000 deaths. Moreover, with cholera prevailing in parts of Europe during the present year, the epidemic in the Ukraine having been the worst experienced for ten years, and on account of the difficulty in the detection at quarantine stations of the cholera carriers by whom cholera is so often introduced into a community or country, it is important that every standard work upon therapeutics should place at the disposal of the physician the most recent facts regarding the proper treatment of this disease, particularly because, while there is no specific remedy known for Asiatic cholera, probably more lives can be saved by early and careful attention to the details of treatment in cholera than is the case of almost any other infectious disease for which a specific is not known.

While some authorities upon Asiatic cholera have emphasized that the treatment of this disease must aim at (1) the destruction and removal of the cholera vibriones from the body, (2) the neutralization of the toxins, (3) the prevention of secondary infections through the damaged mucosa of the intestine, and (4) the relief of unfavorable symptoms, we nevertheless know to-day that we cannot by any known treatment accomplish anything of importance in regard to the first three of these measures. What, however, we can hope to accomplish by direct treatment is to replace the great loss of fluid from the body which occurs so commonly in cholera, and prevent the occurrence of uremia. In order intelligently to understand the treatment of the disease, it is necessary to be familiar with the nature of the toxin the cholera spirillum produces, the manner in which this organism exerts its pathological effects, and the character of the immunity which results from the infection.

Cholera Toxin.—There has in earlier years been considerable difference of opinion in regard to the exact nature of the cholera toxin, and as to whether the cholera spirillum produces a true soluble toxin similar to that, for example, of the diphtheria bacillus. Although extensive studies have been carried on in this connection, it has not been possible to show that the organism produces such a soluble toxin, or that we are able to produce a powerful antitoxin serum which neutralizes toxin and which at the same time follows Ehrlich's law of multiples. On the other hand, from a consideration of all the experimental evidence, it seems evident that the toxin of the cholera spirillum exists as a constituent of the cell or as an endotoxin and becomes soluble only through the disintegration of the cholera spirillum. The results of the author's experimental work on this subject, carried on at intervals through a period of over twenty-five years, have been in accord with this view.

If eighteen-hour agar cultures of the cholera organism are suspended in sterile normal saline solution, filtered through a Reichel candle, and the filtrate injected into guinea pigs in varying amounts, it will be observed that the filtrate possesses very little toxic power. On the other hand, if what remains on the filter is suspended and injected, even though the organisms are killed before injection, the animal dies with all the symptoms of cholera intoxication. Evidently the bacteria contain the toxin. If other agar cultures of the organism suspended in saline are carefully killed, for example, by heating for a brief period, and the bacteria are allowed to digest themselves by their own ferments for two or three days, ground in a mortar, and then filtered off, the filtrate obtained from these killed and digested organisms when injected into animals shows marked toxic properties. The filtrates of very young bouillon cultures of the cholera organism are also not toxic for animals, and only in filtrates of those cultures in which there are found numbers of dead bacteria, which through autolysis have begun to disintegrate, is a toxic action observed. The filtrates of old bouillon cultures are much more toxic. Obviously all of this evidence is in favor of the view that the cholera toxin is an endotoxin, and experiments in immunization which have been made also support this view.

During the past year Sanarelli has again studied the nature of the cholera toxin. He submitted a culture of the cholera vibriones to 0.1 per cent solution of sodium carbonate, and a 1 : 100 pancreatin solution. The bacteria were then killed by a few drops of toluene. Through the action of the pancreatin the vibriones were dissolved and the toxin liberated. He found that this toxin gave rise to the same pathological effects in animals as the living vibriones. It is not necessary, however, to employ either the sodium carbonate solution or the pancreatin to dissolve the vibriones for this purpose. The writer has previously demonstrated that the cholera vibrio possesses its own ferments which are capable of digesting the organism, and if the spirilla are merely suspended in saline solution autolysis occurs and the toxin is set free.

Bail recently found that a watery extract of cholera vibriones were rendered atoxic by guinea-pig leukocytes, and that the leukocytes themselves combined with the toxin and did not part with it on transference to the peritoneal cavity of a guinea pig. An extract of the leukocytes could not be shown to possess protective power. The cells and toxin apparently combine according to the law of multiples. With the aid of this simultaneous injection of leukocytes and extract, it was possible to immunize guinea pigs actively and obtain a serum with a considerable degree of antitoxicity, but used therapeutically the serum only protected effectively against the acute effects of a cholera toxin injection. A lethal marasmus usually supervened about the fifth or seventh day. He found it impossible to immunize rabbits actively in the way it was possible to do with guinea pigs. By the same procedure he immunized a sheep and found its serum capable of protecting against a watery extract of cholera toxin according to the law of multiples and to some extent against infection with the living organism. Further experiments with such a serum have apparently not been made.

Pathological Effects of Cholera Spirillum.—In the stage of evacuation, which follows the incubation or premonitory stage in cholera frequently within a few hours, several quarts of fluid containing salts may be passed from the intestine or from the stomach by vomiting. This brings about an extreme dehydration of the tissues and blood, a fall in blood-pressure and surface temperature, marked weakening or disappearance of the pulse, shrinking of the skin, muscular cramps, and suppression of urine. These symptoms are particularly the result of the pathological osmotic processes which occur during the course of the disease. In relation to the loss of fluid from the body there is: (1) an osmotic current from the vessels into the intestinal canal; (2) a current from the corpuscles into the surrounding fluid; and (3) a transit of the fluid from the tissues into the vessels. In this way the blood becomes profoundly altered, physically and chemically.

The change in the constituents of the blood has been shown by Schmidt and Aron to occur in the following order; the water transudes before the solids of the serum; the inorganic before the organic solids; the chlorids before the phosphates; and the salts of soda before the salts of potash. Shorten has more recently confirmed this retention of phosphates in the blood and Segale has shown that glycogen disappears from the blood and that there is a mere trace left in the liver. The alkalinity of the blood becomes gradually diminished and the percentage of chlorid in the serum in some of the most severe cases is greatly reduced. Hence the blood in the acute stages of cholera is found to be of high specific gravity, very dark, and deficient in water and salts, the cells and albumin being in excess. The amount of oxygen in the red cells is greatly diminished. The severe purging and vomiting having brought about a concentration of the blood, the red corpuscles are found to be increased, and there is a corresponding rise in the precentage of hemoglobin. Usually also there is a leukocytosis. Urea has been found in the blood in fatal cases in the algid stage, but the cholera toxin has not been detected in the blood. There is then, particularly in the stage of collapse, an almost invariable loss of water from the blood which is accompanied by a corresponding loss of salts, particularly chlorids. This water loss is constantly high in the blood of persons who have died of the disease. In the later stages of the disease the blood again shows an almost normal content of water, but the salts are not replaced in the normal amount and proportion. Therefore the blood at this stage has a diminished salt content and is hypotonic, and its alkalinity is usually reduced. These changes are obviously of particular importance in reference to the treatment of the disease.

Immunizing Properties of Cholera Immune Sera.—Although it has not been possible to secure a serum with high antitoxic power against the cholera endotoxin, anti-endotoxic sera have been prepared and their action studied by a number of investigators. Thus Metchnikoff, Roux, and Salimbeni, of the Pasteur Institute, Paris, after three months treatment of horses and goats with the cholera toxin, found that the serum of the animals was effective in amounts of 3 c.c. against one and one-half times the lethal dose. Brau and Denier, of the Pasteur Institute of Saigon, found that guinea pigs and rabbits could be immunized against the toxin so that they were able to resist two fatal doses injected at one time, and horses which had been inoculated intravenously at intervals of six months with 0.5 liter of the toxin, furnished a serum of which 0.02 c.c. neutralized two fatal doses of the cholera toxin after a contact of thirty minutes in vitro.

MacFadyan undertook experiments with sterile juices obtained from the cholera organism, the bacteria being ground at the temperature of liquid air, so as to preclude the possibility of chemical change, the organisms then being placed in ten times their weight of 0.1 per cent liquor potassii. Toxic extracts were obtained from the most virulent cultures which killed guinea pigs acutely in doses of 0.1 to 0.5 c.c., while 0.02 c.c. rendered the animals ill. The endotoxin also exerted its action when injected subcutaneously in quantities of 1 and 2 c.c. Doses of 0.1 and 0.5 c.c. killed rabbits on intravenous injection. Goats were immunized with increasing doses of the endotoxin and a serum was obtained of which

0.002 c.c. neutralized from three to four ascertained lethal doses of the endotoxin for a guinea pig.

Kraus prepared a serum for the treatment of cholera by inoculating a horse with cholera toxin at intervals of from 6 to 8 days during a period of ten months until 900 c.c. of toxin were injected. With such a serum he succeeded in saving mice which had received one hour before the toxin or been infected with the cholera spirillum. In guinea pigs, if the injection of the serum was delayed for one-half hour after the injection of the toxin or of the infection, even large quantities of the antitoxin would not save the animal. Through the intravenous application of large doses of the serum guinea pigs could occasionally be saved after one-half hour, but after one hour it was of no value.

The writer also in Manila prepared an anti-endotoxic serum by the inoculation of an extract of the cholera organism made by killing the organisms carefully within a very brief period, digesting at 37° C., grinding, and submitting the suspension to a pressure of about 600 atmospheres, and, finally, filtering through a Reichel or Berkefeld candle. In this way sera were obtained of which 0.2 c.c. would neutralize four lethal doses of toxin when mixed immediately before inoculation.

It is important to note that in none of these sera produced by experienced investigators in well-equipped laboratories in different parts of the world was the antitoxic power sufficient to neutralize more than four lethal doses of the toxin. In the writer's experience, if the lethal dose was further increased, the animal succumbed to the effects of the toxin, even though the antitoxic serum was given in much larger amounts. It is equally important to emphasize that when cholera immune sera are prepared by repeated inoculations of an animal with killed or living agar cultures of the cholera organism, the properties which such a serum exerts in its protection of a susceptible animal are mainly bactericidal. If a guinea pig is inoculated intraperitoneally with 1 loop of a virulent cholera culture (of which the lethal dose is .1 loop) and at the same time or a little later the animal is inoculated in the same manner with a cholera immune serum obtained as indicated above, the cholera organisms are quickly broken up and destroyed and the animal survives the infection. If, however, the inoculation of the serum is delayed for one or two hours after the time of the infection with the living vibrio, then, even though very large doses of the serum are given, the animal dies of intoxication. In this instance, although the great majority of the vibriones are disintegrated and destroyed by the serum, the organisms have increased so rapidly in numbers that when they are destroyed sufficient endotoxin is elaborated from the bacterial bodies, together with that which results from the few surviving organisms, to cause the death of the animal later. If the injection of the serum is delayed until several hours after the inoculation with the living organism, that is, until a time when the animal is beginning to suffer from intoxication, then, even though very large amounts of the serum are injected, practically very little destruction of the bacteria occurs, owing largely to the lack of suitable complement in the serum of the guinea pig. In spite of this failure, however, nothing will save the animal, not even the addition of fresh complement, since there is already at the time sufficient endotoxin present in the vibriones to cause the death of the animal, and the serum possesses no antitoxic properties in sufficient amount to neutralize the effect of the endotoxin. Moreover, if one first kills, for example with chloroform, the same virulent cholera organism, and inoculates the guinea pig intraperitoneally with the lethal dose of the killed organism (about 4 or 5 loops), simultaneously with the immune serum, although a union occurs between the bacterial amboceptors of the serum and the corresponding receptors of the vibriones (a fact demonstrated by other experiments), nevertheless the animal dies for the same reason expressed before, namely, that a lethal dose of cholera endotoxin in the bodies of the dead organisms becomes liberated by their disintegration, without there being sufficient antitoxin in the serum to neutralize the action of this endotoxin.

If such difficulties then are encountered in attempting to save guinea pigs from cholera infection by such cholera immune sera, it might be accepted a priori that but little benefit would be obtained from their use in the treatment of cholera in man, even though the symptoms of cholera infection are so unlike in these animals and man.[1]

In man also the small intestine offers a more favorable location for the development of the cholera vibriones, and one where the serum has not the same opportunities for coming into actual contact with the developing organisms and exerting its bactericidal properties to the same extent as it can in the abdominal cavity of the guinea pig. Even though in the guinea pig it is also true that in the animals which live for several days after peritoneal infection (without serum) the vibrio infection extends to the mucosa of the intestinal tract, and the vibriones are excreted from it, such action is insignificant in animals which die of intoxication through peritoneal absorption within twenty-four hours of the time of intraperitoneal infection, as well as in those which recover from the destruction of the vibriones in the peritoneal cavity by immune serum. Hence in the experimental infection in the peritoneal cavity of the guinea pig, the opportunities for the favorable action of the cholera immune serum are probably much greater than in cholera in man, and, so far as the action of the serum in destroying the vibriones or in neutralizing the toxin is concerned, the abdominal cavity of the guinea pig would appear to be sufficiently satisfactory for such a test. Moreover, even the fact that the serum in man may be given in greater quantities and is excreted in larger amounts from the intestine will not give it the same advantage of action in this respect as it would have in the abdominal cavity of the guinea pig, and, in fact, it has been shown that, in cases of cholera with symptoms of marked intoxication, the use of these bactericidal sera has not produced any apparent beneficial effect.

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[1] Attempts at cholera infection of young rabbits or monkeys by the mouth have not produced sufficiently definite results to be of any value in the consideration of this question.

Likewise it seems probable from the evidence at hand that in the human body during an attack of cholera anti-endotoxin is produced more slowly and in less amount than bactericidal substances, and, as we have not been able to produce a satisfactory anti-toxic serum, treatment must be particularly directed towards conserving as far as possible the normal processes of the body to withstand the shock of a large amount of endotoxin absorbed within a relatively short period of time. After this period the activities and number of the cholera organisms are greatly diminished in the intestine and recovery is likely to occur unless the absorption of endotoxin has already given rise to the production of pathological processes or lesions of a fatal character. Treatment aiming to conserve or restore these normal processes of the body disturbed during the cholera attack will now be considered.

TREATMENT

Symptomatic Treatment.—In a typical case of Asiatic cholera, it is often possible to distinguish certain well-marked stages of the disease in which the clinical features vary greatly. Thus in a large number of instances a brief premonitory or incubative stage can be recognized, followed by a stage of evacuation in which purging, vomiting, and muscular cramps are the most prominent symptoms. This condition is superseded by one of collapse, and, should the patient survive longer, a period of reaction takes place in which a rise of temperature occurs and, if no complications supervene, the case may end in recovery.

For this reason it is convenient to discuss the treatment of cholera separately for each of these clinical stages, bearing in mind, however, that throughout the course of the disease the treatment must above all be symptomatic. It is important that the cholera patient receive treatment from the onset of the infection, and everything that is possible should be done to preserve his strength.

Sufficient stress has often not been laid upon the treatment of the first stage of the disease, namely, the incubative one. During epidemics the people should be advised to seek medical attention upon the appearance of any gastro-intestinal disturbance. If the patient comes under observation in the first stage, in which diarrhea is the most definite and common symptom, he should be immediately placed at rest and kept in bed, the evacuations being received in a bed-pan. He should be undisturbed by unnecessary bathing, changing of bed linen, etc. It is particularly desirable that he should not be moved. An attempt should be made to check the premonitory looseness of the bowels. No food should be allowed other than rice or barley water. Morphin gr. ¼ with atropin gm. 0.01 (gr. 1/150) hypodermically, or chlorodyne, minims 15 by the mouth, have been recommended, and during the first twenty-four hours are often of service. Beyond this time these drugs should not be administered. It has been asserted that if the diarrhea is arrested and the intestine set at rest, for example, by some form of opium, a better opportunity is offered for the cholera spirillum to multiply and elaborate its toxin. Actually, however, such a condition does not seem to result, and while opium should not be employed in the later stages of the disease, its use is not contraindicated during the incubative stage. Long experience with the use of castor oil, neutral salts, and other purgatives, including calomel, has demonstrated that treatment with these drugs frequently, if not usually, exercises an unfavorable influence over the course of the disease. In the human intestine the cholera organism multiplies most rapidly in a fluid medium; moreover, the action of these purgatives tends to increase the catarrhal condition and to impair the resisting power of the mucous membrane of the intestine. Therefore, the purgative treatment during this stage cannot be recommended, and the indications are to limit peristalsis and to put the intestine at rest. Practically all the intestinal disinfectants that could be tried by the mouth have also been made use of during the premonitory stage but so far without satisfactory result. Either these substances become too dilute before they reach the organism in the lumen of the intestine or the bacteria have already penetrated too deeply into the glands of the mucosa for the disinfectants to reach them. Formerly calomel in divided doses continued for one or two days was recommended by several authorities. Rogers previously employed a single dose of chlorodyne followed by astringent remedies, such as kino and dilute sulphuric acid. More recently he has recommended permanganate of potash. He believes that the permanganate acts by oxidizing the cholera toxins, thus destroying or rendering them innocuous. The quantities given, of course, are too small to destroy the organisms themselves. He advises that the permanganate of potash be powdered finely, mixed with kaolin and made up with vaselin into 2-gr. (0.12-gm.) pills, and then coated with melted salol, or 1 part of salol with 5 parts of sandarac varnish, or with keratin. It is said that these pills dissolve in the small bowel and give off the permanganate slowly without irritating the mucous membrane. In acute cases 2 gr. (0.12 gm.) may be given every quarter of an hour for the first two to four hours, and then 2 gr. (0.12 gm.) every half hour, until the color of the stool changes to greenish or yellow. As much as 50 to 100 gr. (3.25 to 6.5 gm.) of permanganate have often been given by him in the course of from twelve to twenty-four hours. He has also used solutions of permanganate given to the patient to drink, but he remarks that the patients sometimes object to the astringent taste of the drug. It has not been determined, however, that the permanganate given in this way has sufficiently destructive action upon the cholera organism or its toxin in the human intestine to exert any favorable influence on the patient. Long experience has demonstrated that it is better not to administer by the mouth anything that is not essential for the patient, and that the best results are to be obtained by bringing about as complete a rest of the intestine as possible. Confirmation of this idea may be seen from a study of those cases of cholera in which surgical procedures were adopted and, where the abdomen and intestine were opened, a hollow sound introduced and the intestines washed out with a disinfecting fluid. Only unfavorable results were obtained.

Recently a suspension of aluminium silicate (kaolin) by the mouth has been particularly recommended by several observers from the onset of the cholera symptoms and throughout the course of the disease, especially with the idea of preventing the absorption of the cholera toxins from the intestinal tract. More extended reference to the employment of this substance will be made later in the article.

The premonitory stage of cholera, particularly during epidemics, may either be overlooked or be absent, or, at all events, when the patient reaches the hands of the physician, this stage has frequently been passed and that of evacuation already begun. During this period of the disease, as mentioned, purging and vomiting are the most frequent symptoms. Hot fomentations and mustard plasters applied to the abdomen and small pieces of ice given internally may be of some value in checking the vomiting. All medicine by the mouth, with the exception sometimes of dilute solutions of cocain, 1/8 gr. in 1 teaspoonful of water, are of little avail; alcohol is contra-indicated; washing out of the stomach has given rise to no good results and even attempts to remove by means of gastric irrigation the cholera poison, which it has been claimed by some observers is excreted by the gastric mucosa, have failed. The treatment in this stage, therefore, resolves itself into an attempt to secure as complete physical and physiological rest for the patient as possible, and to conserve the body heat by hot-water bottles rather than by too heavy bedclothing. The cramps in the muscles frequently require treatment by massage or brief inhalations of chloroform.

The majority of cases during epidemics come under observation of the physician in the stage of copious evacuation or of collapse. The great problem in this stage is to restore or maintain the circulation, and, if this can be done successfully and the functions of the kidney maintained, recovery will usually occur. During the stage of collapse, or even when it seems likely to occur, opium should never be employed since it may add to the factors which produce anuria later in the disease. During the stage of collapse the pulse, the blood-pressure, and the specific gravity of the blood furnish the most important indications for treatment. If the pulse in the radial artery is present and the blood-pressure not too greatly reduced, the patient requires little treatment beyond that to conserve the body heat. If, on the other hand, the pulse loses volume and power and becomes weak and thready, stimulants, preferably strychnin, hypodermically, are indicated. If the pulse disappears at the wrist more urgent action is called for.

Intravenous Injections of Saline Solution.—By far the most valuable treatment of all in the stage of collapse consists in the intravenous injection of saline solution, which should be administered in all grave cases. If no response is obtained from the hypodermic administration of strychnin, ether administered in a similar manner may be necessary in the interval before or during the introduction of the saline solution. Over half the cholera cases in severe epidemics require intravenous infusion for collapse. After the intravenous injection of salt solution, even in cases in profound collapse, provided a sufficient amount has been introduced, the pulse returns at the wrist, the face loses its pinched expression, the tissues lose their shrunken appearance, cyanosis disappears, and warmth returns to the skin. The pulse and blood-pressure must sometimes be the indicator of the amount to be introduced. When the pulse reaches sufficient volume and the blood-pressure has been restored, injections should be discontinued. Obviously the saline injection should not be carried to a point where the pulse becomes too bounding and the blood-pressure is increased much beyond its normal limit.

In cases of moderate severity, 2 liters of saline solution may be injected within twenty to thirty minutes time, and it will often be necessary to repeat the injections at intervals of from six to eight hours throughout the day and night. The question will arise as to whether the saline solution should be given intravenously or subcutaneously. If there is no radial pulse to be distinguished, the injection should unquestionably be given intravenously; in such instances subcutaneous injections cannot be absorbed in time to be of any value, and, when the subcutaneous method of injection fails entirely, the intravenous method sometimes gives excellent results. The writer has not observed serious results when the solution has been injected judiciously. The intravenous injection may be supplemented later by subcutaneous injections, and in mild cases copious saline enemata alone may be given frequently. Perhaps nowhere in medicine do we see the beneficial effects of treatment demonstrated to a greater degree than in the proper employment of intravenous injections of saline solution in the state of collapse in cholera. Many lives are apparently saved by this procedure, and the mortality of cholera can undoubtedly be reduced by this method of treatment. However, in the great majority of cases after intravenous injections, the purging returns often accompanied by the other symptoms of the stage of collapse. Hence constant attention must be paid to the pulse and to the blood-pressure or specific gravity of the blood [2] in relation to the reintroduction of saline solution. Sometimes it is necessary to continue transfusion at intervals during a period of forty-eight hours or longer.

The other treatment of the stage of collapse consists chiefly in stimulation as indicated by means of full doses of strychnin, by conserving the body heat, by allaying thirst by sips of iced water, and by treatment of the distress and pain. However, hypodermic injections of morphin should only be employed in cases with severe pain after other measures such as the application of heat, massage, and even brief inhalations of chloroform have been unsuccessfully tried.

Profound cyanosis and apnea are other symptoms which may occur during the stage of collapse which require speedy and special treatment. These conditions may be brought about partly by the spasm of the pulmonary arteries, the lung refusing to transmit the thickened blood. Frequently only by immediate action can such a case be saved, for, after coagula have developed in the right heart, death is inevitable. The administration of nitrite of amyl or nitroglycerin to overcome the spasm of the pulmonary arteries, together with rapid intravenous infusion of saline solution, is urgently indicated in cases with such symptoms.

Rectal Administration of Saline Solution.—During the stage of collapse the first important decision to be made in treatment is whether the saline solution shall be given intravenously, subcutaneously, or per rectum. Unless the clinical appearance or the blood-pressure demand the intravenous injection the solution should be given per rectum. No case should receive an intravenous injection unless the indications are decidedly in favor of such treatment. The indiscriminate use of intravenous injections of saline in cholera is dangerous. Greenwald has recently shown that all sodium salts injected in excess are toxic and that there is produced a sudden and marked disturbance of the relation between sodium ions and other cations. It should also be borne in mind that after intravenous injections the return of the symptoms of evacuation is usual. Even in severe cases where it is necessary to give intravenous injections, it is also advisable that injections of fluid per rectum be given. In the stage of evacuation much of the fluid will be rejected, but some is usually retained, and in mild cases the need of intravenous injections is often avoided. One-half liter of the saline or alkaline solution may be given every two hours until the collapse stage is passed.

Other Treatment in the Collapse Stage.—In addition to the above methods of treatment, much fluid may be taken into the system by the mouth. It is useless to give large quantities at a time on account of the vomiting, but by allowing an ounce or two at a time, with short intervals, the patient will frequently retain a large amount. When the temperature in the rectum is not below normal, ice may be given to suck. Dilute acids, both mineral and organic, have been recommended from time to time in the treatment of cholera, but this method of treatment has been generally given up as being of no advantage. The permanganate treatment has already been discussed.

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[2] The estimation of hemoglobin by an accurate method serves the same purpose as the estimation of the specific gravity of the blood.—Editor.

As already mentioned, aluminium silicate (kaolin) has recently been employed by several observers who have claimed very good results from its use. Thus Kühne, in the recent epidemic of cholera during the Balkan Wars, has claimed to reduce the mortality in this disease from 45 to 2 or 3 per cent by treatment with this preparation. Braafladt also employed this substance during a severe epidemic of cholera in China. In three series of cases treated by different methods the results were as follows:

1. Patients given hypertonic saline treatment, mortality 22 per cent. Convalescents discharged on the eighth day.
2. Kaolin and hypertonic treatment, mortality 29 per cent. Convalescent patients discharged on the sixth day.
3. Kaolin treatment only, mortality 1 patient in 35 cases (this patient died of gangrene of the uterus after miscarriage). Convalescent patients discharged after four days.

All these patients had true cholera vibriones isolated during their stay in hospital.

Walker treated a series of 75 cases in one village in China with no fatal results, and this in spite of the fact that many of the patients arrived in a condition of extreme collapse. Crawford, in China, and Mendelssohn, in Saigon, during the past year have each also had a slightly lowered mortality in cases of cholera treated with kaolin as compared with intravenous treatment. Walker has recently emphasized the advantages of the kaolin treatment and advises this method on account of its simplicity, the absence of relapse in cases treated with it, cessation of loss of fluid, early return of passage of urine, and rapid convalescence. He believes the treatment of particular value on account of the adsorption of toxins which it produces. The action of kaolin is apparently twofold: the first, mechanical, and the second, adsorptive. The substance is not bactericidal and does not destroy the cholera vibriones. The first result of its administration in cholera is said to be the cessation of vomiting, which seems to be due to the adsorption of the toxic substances in the upper alimentary tract. This is followed by the cessation of diarrhea and consequent loss of fluid, also presumed to be due to the presence in the bowel of irritant toxic substances and these being adsorbed by the kaolin cease to act as an irritant. It is also believed that the presence of a layer of kaolin on the intestinal mucosa appears to act in part as a filter bed, preventing the transmission of toxins to the patient. It has been experimentally demonstrated that the toxin of the cholera vibrio will not pass through layers of kaolin, at least in an active state. The method of treatment recommended by Kühne is to place 100 gm. kaolin in ¼ liter of water and to allow the patient to take a glassful, cold, every hour or half hour. According to him it is rarely necessary to take more than six glasses, about 200 gm. of kaolin, in the first twelve hours. During the second twelve hours and the following day he recommends several glasses of the mixture. Should the case be so severe that the stomach and intestines are atonic, the mixture must be given either by stomach pump, or, if this is not possible, as an enema. He emphasizes the fact that during the eighteen hours which follow the beginning of treatment, except for water, neither food nor drink should be given. Walker has recommended that a large supply of half and half suspension of kaolin in water be placed near the patient, and that he be encouraged to drink as much as possible. At first large quantities can be tolerated but, as the vomiting and diarrhea cease, the liquid is refused. It is desirable that this substance should be more extensively tried in severe epidemics of the disease.

Mukarji has found that limewater is inimical to the growth of the cholera vibrio if used in sufficient quantity and it has been suggested that it might be used as a vehicle for kaolin.

Treatment of Anuria and Uremia.—By far the most important symptom requiring treatment in cholera, apart from the stage of collapse, is that of anuria, and the restoration of the urinary excretion is the most important symptom in determining the prognosis after the patient has survived the collapse.

It is particularly interesting to recall the statistics collected by Rumph and Frankel in relation to this symptom. Of about 700 cases of cholera in which no anuria existed, even in the first days of the attack, although the urinary secretion was considerably diminished, only about 4.7 per cent died. In 1,000 cases in which anuria was observed, 57.2 per cent died.

In this connection it is important to recall that in the stage of evacuation the local effect of the spirilla in the intestinal mucosa, which is manifested by severe catarrh, may be sufficient to explain some of the intestinal symptoms, such as the copious exudations, the violent diarrhea, and perhaps vomiting; but the heart failure, cyanosis, and nephritis, and other accompanying symptoms, which also result cannot be explained in this manner. These differences may be brought about, first, by the enormous abstraction of water and salts both from the blood and from the tissues, and, secondly, by the action of toxic substances produced by the cholera spirillum and absorbed from the intestine. The qualitative and quantitative changes in the blood have already been mentioned and need not be referred to again here. Just how much the anuria and subsequent nephritis occurs as a result of the abstraction of the water from the blood and tissues and just how much they are due to the action of the cholera toxin is not altogether clear. However, it seems unquestionable that the abstraction of such enormous amounts of water from the tissues, resulting as it does in the increased thickening of the blood, its loss in volume and consequent rapid fall of blood-pressure, must play a very important rôle in the production of the collapse, and, consequently, in the interruption of the blood supply of the kidney, with resulting damage to its parenchymatous cells. It is interesting to recall that when guinea pigs are inoculated intraperitoneally with lethal amounts of cholera spirilla, although the organism passes through the peritoneum to the intestinal mucosa of the animal, there is no purging, and hence no great loss of fluid; however, while before death in the animals a condition of shock is brought about, with rapid pulse and progressive lowering of the temperature (undoubtedly due to the action of the cholera toxin), after death has occurred no such advanced lesions of nephritis are encountered as are seen in the kidneys of human cases of cholera, which have succumbed after symptoms of anuria.

If, therefore, as seems probable, the disturbance of the circulation plays such an important part in the production of the anuria in cholera and the subsequent nephritis, it seems still more important for us to watch and restore the circulation in the treatment of this disease and make good as early as possible the loss of fluid and thereby prevent at least some of those pathological changes which must result in the parenchyma cells of the kidney if the blood supply is even temporarily interrupted in this organ. Once the circulation in these organs has been profoundly disturbed, the restoration of their function becomes a much more difficult problem to treat, as does also the resulting uremia which so frequently follows.

Coffee in small amounts by the mouth, if it can be borne by the patient, may be of some slight benefit during this stage of the disease in stimulating the action of the heart and kidneys, and digitalis is sometimes indicated. Stimulating diuretics in general, however, should not be employed in cholera uremia. Their use is of doubtful benefit and they frequently do harm. Cupping, sweating, and hot packs are not to be recommended for the treatment of the uremic symptoms.

Recently Sellards has emphasized the fact that the relief of uremia in cholera is intimately connected with the problems concerning the treatment of acidosis. In the study of the urine in this disease, he found an almost constant increase in the excretion of ammonia, and that cholera patients showed a distinct tolerance to alkalis, that is, a considerable excess of sodium bicarbonate was required to render the urine alkaline as compared with normal individuals. Thus he found that even after relatively enormous injections of bicarbonate of soda (90 gm.), the urine of cholera patients sometimes remains sharply acid, in normal individuals a small amount (3 to 5 gm.) being sufficient to change the reaction of the urine from acid to alkaline. More recent investigations demonstrated that this tolerance to bicarbonate is due to an acidosis or more correctly to a deficit of the body in fixed bases. The acidosis in cholera is obviously not specific but is similar to that observed in nephritis and uremia from other causes. From the results of the tests of tolerance to bicarbonate in cholera, it was demonstrated that acidosis usually made its appearance early in the stage of reaction of the disease, and that the degree of acidosis increased rapidly and reached its maximum in those cases showing the most marked evidences of uremia. Very satisfactory results were obtained in the relief of this uremia by treatment with alkalis. Rogers and Shorten later confirmed these observations and demonstrated that a greatly reduced alkalinity of the blood is a constant feature of severe cholera, the alkalinity of the blood often being reduced from a normal of about N/25 to as low as N/60 to N/80 and, in cases terminating in fatal suppression of urine, to N/100 and even lower. Such extreme cases of acidosis are always fatal.

Reference has been made to the importance of carefully watching the pulse, the blood-pressure, or the specific gravity of the blood in connection with the administration of saline solutions, and it is also important to observe the reaction of any urine that is passed or that is obtained by catheter in connection with the administration of sodium bicarbonate solution.

Indications for Intravenous Injections.—In order to treat cases intelligently by intravenous injection of saline and bicarbonate solutions, it is necessary briefly to recall the changes in the blood which take place in this disease. The pathological osmotic processes and the loss of water and salts have already been referred to. The loss of fluid from the blood is obviously of particular importance in such treatment. In the mildest cases of cholera not requiring transfusion, there may be a loss of about one-third of the serum of the blood. In moderately severe cases requiring transfusion, and eventually recovering, the loss may amount to about half, while in the most severe fatal cases the loss may average almost two-thirds of the fluid of the blood. This may be demonstrated in a simple way by centrifugalizing in the hematocrit small amounts of defibrinated normal blood and blood from cholera cases, and measuring and comparing the percentage of corpuscles and serum. There is, then, a marked relationship between the severity of the symptoms of the disease in the acute stages and the percentage of fluid lost from the blood. In all but the mildest cases, from one-half to two-thirds of the fluid of the blood, and probably a similar amount also from the tissues, may be lost. So the necessity of replacing this amount of fluid is clearly indicated, and the favorable results when this is done are evident from the improvement in the condition of the patient.

Rogers has recommended the specific gravity of the blood as a guide to transfusion in cholera. It has long been known that the specific gravity of the blood rises markedly in this disease, but until recently this change has not been observed carefully in relation to the treatment. The determination of the specific gravity of the blood he believes constitutes a rapid and readily available method of ascertaining the amount of fluid which has been lost from the blood in cholera cases. He has employed for this purpose the Lloyd-Jones glycerin and water specific gravity method as well as the hematocrit estimations of corpuscles and serum already referred to. In this connection he uses the following simple rule for treatment. If the specific gravity of the blood is raised from normal of 1.056 to 1.058 up to 1.063 then 1.7 liters of salt solution can safely be injected; if it is 1.064 then 2.25 liters, and if 1.065, 2.8 liters may be given, while in adult males with even higher specific gravities of the blood, 3.4 liters have been frequently used by him with great advantage.

The method of taking the specific gravity of the blood is as follows:

A number of solutions of glycerin and water are prepared with specific gravities varying from 1.040 to 1.076. These may be kept in stoppered bottles and should vary from two to three degrees apart. From these stock solutions a small number of stoppered bottles holding a few cubic centimeters are filled and taken into the ward. A small drop of blood of the patient obtained in a capillary tube is then placed in the middle of one of the bottles of glycerin solution of about the specific gravity which it is expected to find. If it rises it is obviously lighter than the fluid, and another drop is placed in a bottle of lower specific gravity, or vice versa, until the one in which it just floats for a second or two is found. If it has been found to rise slowly in one and sink in the next solution, the correct specific gravity will be between that of the two solutions.

If the specific gravity is over 1.065 it is usually advisable to give an intravenous injection, even when the general condition of the patient does not appear to demand it, as any further loss of fluid is liable to induce sudden and dangerous collapse. It is well also to take the specific gravity shortly after the transfusion to see if the blood has reached about the normal concentration. Should collapse recur, or if it should appear at all likely to recur, the specific gravity should again be taken. If the specific gravity is raised to over 1.060 and the blood-pressure is also low, then a copious intravenous injection can also be safely given.

Another point of importance in relation to intravenous therapy in

Asiatic cholera is the question of the blood-pressure which is usually below 70 mm. at the wrist in the majority of cases. In extreme collapse it is too low to be measured at all at the wrist. Such cases form about one-third of the admissions to hospitals, as a rule. In native Malay patients the normal systolic pressure usually varies from about 100 to 120 mm. of mercury. When collapse occurs and the blood-pressure is below 70 mm. in natives and 80 mm. in white persons, it is advisable to replace the lost fluid and salts by a sufficient amount of fluid to raise it to normal, in order to attempt to insure a rapid excretion of the toxin through the kidneys. One should continue to observe the blood-pressure during the disease and to maintain it at a point which will tend to promote a free excretion of urine. A systolic blood-pressure of below 70 mm. is usually an indication of a dangerous degree of collapse. According to statistics kept in India for several years, no patient whose blood-pressure remained throughout at over 70 mm. died in the collapse stage. With a blood-pressure below 70 mm. obviously there is usually a very feeble pulse at the wrist. If one has not the opportunity or means to determine the blood-pressure, as is frequently the case during epidemics, the digital examination of the pulse with reference to its quality and rapidity will of course give some idea as to when the intravenous injection should be given. If restlessness is frequent and repeated cramps exist, and if there is cyanosis of the fingers and the lips, even though the pulse may be felt at the wrist, no time should be lost in attempting to restore the fluid. Commencing restlessness in the acute stage should lead to an examination of the patient's pulse or blood-pressure with a view to transfusion. Suppression of urine for twenty-four hours or more is also an indication for transfusion. Since retention of urine is very common, it is often necessary to catheterize patients frequently. If the urine is strongly acid, intravenous injection of the sodium bicarbonate solution is indicated. If, on the other hand, the acidity is not increased or the urine is alkaline to litmus, the tissues probably possess a sufficient supply of the fixed bases and transfusion of the alkaline solution is not indicated.

Technic of Administration of Intravenous Injection.—The sterilized solution is introduced into a sterilized graduated glass vessel of a capacity of 1 to 2 liters, to which is attached about 6 feet of rubber tubing, to the lower end of which a stopcock and cannula or needle is fitted. After insertion of the needle or cannula into a vein, the glass vessel is elevated and the fluid should be allowed to enter slowly by gravity, usually at about 100 c.c. per minute, the rate of flow being regulated by the stopcock. The amount usually necessary in adults varies from 1½ to 2½ liters.

The veins are often or usually in a collapsed condition in cholera, and sometimes the introduction of a needle or cannula into the vein is performed only with great difficulty. An attempt should first be made to distend the vein with a bandage or rubber tourniquet placed about the limb. Ordinarily the arm veins are the ones which can be used to greatest advantage. I have seen cases not only in children but in adults in which it was impossible to employ these, and then either the internal saphenous, near the point where it crosses the internal malleolus, or other superficial veins of the leg may be employed. Usually it is preferable to employ a syringe needle for puncture, and frequently it is not necessary to dissect out the vein, though sometimes its dissection cannot be obviated. No anesthetic is needed for the operation. The patient is usually far too ill to notice it. In case the vein is dissected out, two ligatures may be passed around it, one of which may be tied about the cannula if this is employed in place of a needle, and both ligatures tied after the operation if necessary. Great care must be taken, of course, in giving these intravenous injections that everything is carefully sterilized.

Composition of Solutions for Intravenous Injection.—With the object of preventing the rapid loss of fluid from the body which generally recurs after transfusion with normal sodium chlorid solution, a number of other solutions have been recommended. There seems to be no doubt that the chlorid content of the blood is decreased in nearly all severe cases of cholera, but in the first three days of the disease, according to the results of Aron's work performed in Manila, we can scarcely speak of a greater loss in the salts than would correspond to that of the water. Reference has also been made to the fact that in the late stages of the disease the blood again shows an almost normal content of water, but the salts are not replaced to the normal amount; therefore, the blood at this stage has a diminished salt content and is hypotonic. Rogers, however, has recommended a hypertonic solution for treatment at any time during collapse. He advises for general adoption for either subcutaneous, intraperitoneal, or intravenous injections the following formula:

Sodium chlorid	gr. 120 (8 gm.)
Calcium chlorid	gr. 4 (0.25 gm.)
Potassium chlorid	gr. 6 (0.4 gm.)
Water	1 pt. (568 c.c.)

During an epidemic of cholera in Manila, Sellards and McLaughlin treated two series of cases, one with isotonic (0.85 per cent) and the other with hypertonic salt solution. The hypertonic solution contained 1.3 per cent sodium chlorid, the calcium and potassium salts being the same as in Ringer's solution. The mortality in the cases treated with the isotonic and with the hypertonic solution was practically the same, and no advantages whatever were demonstrated for the use of the hypertonic solution.

Strauss, believing that hypertonic sodium chlorid solutions in large doses do harm to an already damaged epithelium of the kidney, has advised the use of an isotonic 4½ per cent glucose solution for treatment, and Kauch a 5 per cent solution of glucose for subcutaneous injection and a 10 per cent one for intravenous injection. Bayliss believed that hypertonic intravenous injections of saline solution might be of greater value than those of isotonic strength, owing to the raised salt content preventing by osmotic pressure the escape of fluid into the tissues; nevertheless he recognized that, since the blood-vessel walls were permeable to salts, these passed into the tissues and, the equal concentration being established there, the additional fluid was no longer kept within the circulatory system. He therefore suggested the use of a colloid such as gum acacia which can pass through the walls of the blood-vessels, but does exert osmotic pressure. He recommended solutions of 6 or 7 per cent gum acacia in 0.9 sodium chlorid solution for treatment of hemorrhage and wound shock. He also pointed out that the calcium carbonate in gum acacia would help to neutralize any acidosis, the calcium itself being possibly used for its physiological action. The glucose and gum acacia solutions have been employed to some extent in the treatment of cholera in China and India, but have not been demonstrated to have any particular advantages over normal saline solution. In fact, Rogers has found that the gum acacia recommended by Bayliss is a failure, and he believes that the gum solutions lead to the retention in the circulation of the cholera toxins.

Moore believes that the efficiency of saline solutions in cholera, and the inefficiency of colloidal solutions such as gums may be explained on the ground that the condition is one of excess of toxic colloids and defect of balancing electrolytes or salines. On the other hand, free saline in the blood in cholera combines with toxins to form a crystallocolloidal union, and this is an essential factor in the excretion of the poison by intestine and kidney. The unattached colloidal molecule of toxin possesses no osmotic pressure, nothing to drive it through an excreting cell. When it becomes attached to a crystalloid, the combination acquires a directive force and possesses the power of diffusion. Palmer, Atchley, and Loeb have recently shown that egg-albumin, like gelatin, influences the conductivity of a 0.6 per cent sodium chlorid solution in two ways: (1) at an hydrogen ion concentration of about pH 3.0, increasing concentrations increase the conductivity; (2) near the iso-electric point of albumin and at the pH of the blood, increasing concentrations of albumin decrease the conductivity of the NaCl solution.

For the intravenous injection of alkali Sellards recommended during the stage of collapse a solution composed of 0.5 per cent sodium chlorid and 0.5 per cent sodium bicarbonate. Early in the stage of reaction 1.5 per cent of bicarbonate was substituted without the addition of any sodium chlorid. If the urine does not became alkaline to litmus after the injection, or if the amount of alkali remains small, it is recommended that the bicarbonate be increased to 2 per cent. He found the weakly alkaline solution of 0.5 per cent as satisfactory as the neutral saline for the treatment of the stage of collapse. He emphasizes that it is imperative to use bicarbonate and not the normal carbonate, and that, in sterilizing, certain precautions must be taken on account of the ease with which bicarbonate is converted to carbonate by heat. The bicarbonate solutions may be sterilized in an autoclave in an atmosphere of carbon dioxid, or they may be sterilized in an open vessel and a stream of sterile carbon dioxid passed through the solution after cooling. Rogers recommends that weighed packets of the salt be sterilized by dry heat and added to the previously boiled saline solution. With the use of massive doses of bicarbonate, such as 60 to 90 gm. in twenty-four or forty-eight hours, a prompt and free secretion of urine usually occurs in cholera patients and deaths from uremia are very greatly reduced. Sellards found that patients admitted in advanced uremia with complete suppression of urine usually voided freely after massive injections of bicarbonate, and the restlessness and air-hunger disappeared. While such patients were thus made distinctly more comfortable they nevertheless usually succumbed.

In connection with the study of the treatment of uremia in cholera, it would seem advisable to repeat and extend the recent investigations of Foster regarding the presence of a special toxic substance in the blood in uremia from other sources.

In comparing two groups of cases of cholera, one treated with sodium chlorid solution and the other with alkaline solution, the most important clinical difference noted was the absence of uremia in the group receiving bicarbonate. The only unfavorable results which have been observed from the injection of alkaline solutions in cholera is the appearance sometimes of a moderate and temporary hematuria and mild convulsions. These disturbances, however, have only very rarely been observed, and may have been due to the conversion of sodium bicarbonate to the carbonate.

Greenwald believes that tetany which occurs after large doses of sodium bicarbonate is not due to alkalosis, but to the high concentration of sodium salts. He points out that when the convulsions appear after the injection of sodium carbonate or bicarbonate, the concentration of sodium in the plasma may be the same as when convulsions appear after the injection of sodium chlorid or sulphate. Rogers states that as the use of the alkaline solution produced such a great reduction (70 per cent) in the deaths from suppression of urine, while the reduction in the alkalinity of the blood was found to be constant in severe cases of cholera, he now first gives, in all cases which are treated by injection, 568 c.c. of the sodium carbonate solution unless the urine is found to have been already rendered alkaline.

Temperature and Amount of Fluid for Intravenous Injections.—In making intravenous injections it is important to estimate the right temperature at which the fluid should be injected. In spite of the low surface temperature in the stage of collapse the rectal temperature is rarely below normal and more often above normal. In cases where the rectal temperature is very slightly below or above normal, the fluid should be run in at or as near the normal temperature as possible (99° to 100° F.). In rare cases in which the rectal temperature is a degree or more below normal, the fluid should be at a temperature of 102° to 104° at first, and lowered later when the surface heat returns. If the rectal temperature is much over 100, the solution should be used at several degrees below normal. The determination of the amount of saline solution to be injected in cholera may be made in accordance with the general condition of the patient or the specific gravity of the blood. From 1½ to 2½ liters are usually required in an adult male to replace the loss of water and to give a slight excess, in order to allow for some further loss. If the specific gravity of the blood is over 1,065, from 2½ to 3½ liters may be given. In rare instances an additional half liter may be run in slowly. It is usually safe to lower the specific gravity to 1,050 or even a little lower, but careful watch should be kept for any signs of distress or of increased frequency of respiration, since these symptoms may indicate embarrassed circulation or commencing edema of the lungs. When these symptoms develop, the injection should be stopped at once. In females about 2 liters are usually sufficient, while in children from ten to fifteen years of age about a liter is usually required. Five hundred c.c. can usually be given to a child of five years.

The effect of the injections on the pulse and blood-pressure is also an important aid in judging how much fluid is required. A return of a blood-pressure of about 100 to 110 in native Malays and slightly higher in the white races should be aimed at, and one should not be content with merely feeling the pulse at the wrist, but should continue the injection until if possible a full pulse is obtained. The fluid may be allowed to run in at the rate of 100 c.c. per minute in severe cases. If unfavorable symptoms appear, it should be run in more slowly. Rigors not infrequently follow the intravenous injections. In Manila, collapse was usually overcome in 90 per cent of the cases by the intravenous injections of saline solution repeated as often as necessary. The average number of injections given was two. On the other hand, some cases require as many as ten or twelve injections and subsequently recover after receiving from 20 to 25 liters of fluid. Generally patients which recover show improvement before the third day of treatment.

In cases at Manila treated with intravenous injection of saline, but not with alkali, uremia followed survival from the stage of collapse in nearly one-half of the severe cases. By the employment of injections of sodium bicarbonate the mortality from uremia as mentioned may be very much reduced.

Treatment of Stage of Reaction.—After a patient has survived the collapse stage and has entered upon the stage of reaction, it must be borne in mind that he is by no means out of danger, and also that collapse may recur. The two great sources of anxiety are: (1) that the body temperature rises and hyperpyrexia may occur; and (2) continued failure of the kidneys to secrete may end in uremia. The stage of reaction is usually accompanied by some rise in temperature and the intravenous injections may themselves sometimes give rise to a moderate increase in temperature. For the treatment of hyperpyrexia copious enemata of iced saline solution are recommended. Ice should be applied to the head and cold sponging should be employed until the temperature falls. A surface temperature of over 103.5, and a rectal one of over 104 are indications for such treatment. The patient of course should not be surrounded with hot-water bottles when the temperature is elevated, and indeed these should be used even in the stage of collapse only when the temperature is subnormal. Drugs must not be given or only employed cautiously in the stage of reaction to check the diarrhea, as such treatment seems to lead to an increased absorption of toxins through the damaged intestinal mucous membrane. Opium and lead are particularly dangerous at this stage, as they predispose to the condition of uremia, the treatment of which has already been discussed. Should the tongue be coated and the secretion of bile violently interfered with, the administration of calomel in small doses may be employed. During the stage of reaction, should slight predisposition to uremia continue, alkaline saline solution may be given per rectum by the drop method according to the following formula:

Sodium chlorid	14 gm.
Sodium carbonate (crystallized)	15 to 30 gm.
Water	1,000 c.c.

The temperature of the solution on delivery into the rectum should not be below 105° F. in order to favor retention. When the kidneys begin to secrete freely the concentration of the alkali salts may be reduced. If the uremic symptoms are more urgent, then intravenous injection of alkali should again be employed according to the procedure recommended during the later stages of collapse. In cases in which during the stage of reaction the blood-pressure remains persistently low, pituitrin or adrenalin solution, hypodermically, are sometimes of benefit.

Naame has recently claimed particularly favorable results for adrenalin therapy in cholera giving 4 to 6 mg. per day subcutaneously for several days together with saline intravenous injections. He considers the cholera toxins in severe cases to have an elective action on the suprarenal capsules. He believes the great tolerance shown by the cholera patient toward adrenalin is a sign that an active principle which the disease is destroying is being restored to the organism. Emetin has been recently recommended, but its use has not been shown to be beneficial.

Diet.—During the acute stages of the disease nothing should be given by mouth with the exception of water or rice or barley water. Too early administration of milk, soups, and jellies containing animal albumin is not advisable. Upon resuming food after two or three days, farinaceous ones should be given at first. As long as the kidneys are not acting freely, an increase in the diet should not be made. Patients should be kept in bed for several days after the acute symptoms have subsided, as sudden cardiac failure may occur in patients who sit up before convalescence commences.

Serum Treatment.—The serum treatment so far on the whole has been very unsatisfactory. Indeed, several recent textbooks upon medicine either fail to mention it or dismiss the subject with the statement that such treatment is of little therapeutic value.

On the other hand, the injections of large amounts of the different cholera immune sera have apparently exerted no injurious action, either temporary or permanent, upon the patients so treated with them, and even in those cases in which the functions of the kidneys have been temporarily suspended no injurious effects have been observed from the administration of the serum.

The opinion earlier expressed that the bactericidal effect which the serum would exert in the intestine after intravenous injection might lead to more acute intoxication through the rapid destruction of the spirilla does not seem to be justified from the observations which have been made in relation to the treatment by serum of the disease in man.

Owing to the lack of success from the employment of bactericidal sera in the treatment of cholera, the trend of scientific investigation in relation to the serum treatment of the disease has been in the direction of the preparation of the antitoxic sera, which we have already considered, and the results of treatment in man with these sera will now be discussed.

Treatment in Man.—Brau and Denier prepared two sera for the treatment of cholera in man. Serum A was prepared by injecting a horse with the cholera toxin entirely free from bacteria, and the second one, serum B, by injecting a horse with the living organisms and toxin. These sera were examined by the author, and were found to possess specific agglutinative and bactericidal properties, one showing a much higher value in this respect than the other. No study was made of the neutralizing power of the sera for lethal amounts of the filtered cholera toxin. Guinea pigs inoculated with 1 c.c. of serum B and at the same time with 1 or even 2 loops of a cholera vibrio, of which the lethal dose was 0.1 loop, survived the inoculation; however, when they were inoculated with 5 loops and 2 c.c. of the serum, they invariably succumbed. Pfeiffer's phenomenon seemed to be complete, as was shown by the postmortem examination of a number of these animals, since microscopic preparations from the exudate in the abdominal cavity showed no motile vibriones and the animals had apparently died rather from an intoxication than from an infection. However, these experiments obviously do not demonstrate whether death had occurred from the effect of the endotoxin contained in such a large amount of the spirilla (5 loops) or from the effects of another soluble toxin.

Serum B was found to protect against larger doses of the living organism than serum A, as was proved by testing the bactericidal power of the two sera. The bactericidal value of the sera was apparently, at all events so far as the living organisms were concerned, the most important factor in protecting the animals, at least up to a certain dose. In many of the animals which died and which had not received excessively large doses of the cholera spirillum Pfeiffer's phenomenon was also found to be complete, or almost so.

In all, 52 human cases of cholera were treated by Dr. Denier with the sera. In each instance a careful bacteriologic diagnosis of cholera was made both by Dr. Denier and by the writer. The injections of the sera were given intravenously and in large quantities, as much as 250 c.c. in a liter of Hayem's solution being inoculated at a single dose. Following this primary inoculation 100 c.c. of serum was injected in an equal amount of saline solution every three hours until a reaction on the part of the patient occurred. The average amount of serum given was from 300 to 500 c.c., but in one case 1,000 c.c. was injected in twenty-four hours. The cases in the hospital were treated alternately with serum, that is, every other case admitted received this treatment. The injections of the serum were usually given very shortly after the time of the admissions of the cases to the hospital. Obviously, the patients were frequently in collapse at the time of their arrival. The following table shows the results of the serum treatment:

RESULTS OF SERUM TREATMENT

Injections	Number of Cases	Cholera Spirillum Not Isolated from the Stools	Dead	Recovered	Percentage of Mortality
Controls	21	3	13	5	72
Serum A, antitoxic	16	1	11	4	75
Serum B, antimicrobic	5	..	2	3	40

From this table it is evident that the cases which received the antitoxic serum were not benefited by it, the mortality being even higher than in the ones which received no serum. The number of cases which received the antimicrobic serum is too small to justify decided conclusions, although the mortality is much lower.

The effect of treatment with other of these sera prepared with the idea of possessing antitoxic properties has been particularly observed in the epidemic of cholera in Russia in 1908-1909. Berthenson of St. Petersburg has reported upon 636 individuals who were treated with various cholera immune sera. Those employed were the sera of Kraus, Salimbeni, Schurupoff, and of Kolle, Carrière, and Tomarkin. Of the cases treated with serum 322 died, or a mortality of 51.2 per cent. Since about one-half of those attacked with cholera usually recover with various methods of treatment, the results offer no indication of any value for the serum treatment employed as a whole. Other reports show that 133 cases were treated with the serum of Kraus and of Salimbeni in several different hospitals, and the favorable effect of the serum as employed in these institutions appeared doubtful, according to the reports of Kernig, Ketscher, and Jegunoff. Other investigators, however, believe the serum to have been of value.

Berdnikoff employed the Schurupoff serum in 49 cases in doses of from 40 to 50 c.c. diluted two or three times its volume with physiological salt solution. The injections were usually given intravenously. Only in one group of 10 cases was a distinct favorable action obtained, the mortality being 36 per cent against the general mortality of 70 per cent. In the remainder of the cases treated with the serum no favorable effect was noticed.

Stühlern, however, has reported more favorable results with Schurupoff's serum, particularly when larger doses were used. In the algid stage repeated intravenous injections of the serum were given with a large amount of sodium chlorid solution. The saline injections were also given in intervals between the serum injections, and during the typhoid stage intravenous and subcutaneous injections were combined. In a later communication he summarizes his results in the following table:

RESULTS OF INJECTION OF SCHURUPOFF'S SERUM

Quantity of Cholera Serum Injected, in Cubic Centimeters	Number of Treated Cases	Recovered	Died	Mortality Per Cent
60 — 90	25	14	11	
200 — 400 (390)	79	56	23	..
400 — 600 (590)	27	27	..	..
600 — 800 (790)	26	18	8	..
800 — 1000	19	10	9	..
1040 — 1390	11	6	5	..
Total	187	131	56	29.9

The maximum quantity of serum that was injected intravenously within twelve hours amounted to 600 c.c. In the most severe cases as much as 800 c.c. was injected in thirty-six hours. The cases which were complicated with uremic coma received also subcutaneous injections of the serum, 60 c.c. per day in a course of from five to seven days. Some of the most severe cases received as much as 18 liters of saline solution. One hundred and forty-nine of the 187 cases underwent a very severe attack of cholera with a marked algid stage. Of these 93 recovered and 56 died, a mortality of 37.5 per cent. Twenty-five cases were moderately severe and showed a distinct algid stage; all recovered. In 13 mild cases in which serum was given, all also recovered. In 228 cases which received sodium chlorid solution intravenously and no serum the mortality was 42 per cent, and of 142 cases that were treated with subcutaneous injections of salt solution the mortality was 54.9 per cent.

In a further communication Stühlern reports upon his series of cases treated partly with serum plus physiological salt solution and partly with physiological salt solution alone. Of 742 cases that received neither serum nor systematic intravenous injections of salt solution 407, or 54.9 per cent, died. Of 193 patients who received systematic saline injections but no serum 64 died, or 33.1 per cent. Of 153 patients who received infusions and also serum 46 died, or 30 per cent. He believes that if the cholera serum is prepared in a proper manner it possesses a certain therapeutic effect.

Salimbeni has reported upon 42 cases treated with his serum at St. Petersburg with a mortality of 23.8 per cent, while the general case mortality in the official returns was 45.6 per cent. The serum was injected subcutaneously, as a rule in doses of 100 c.c. in 400 to 500 c.c. of saline solution often repeated. The intravenous injections were given in cases in which the conditions for resorption were not favorable. The author reports that the beneficial results were apparent in the improvement of the pulse and the disappearance of the cramps. In this connection, however, it must be mentioned that such symptoms usually disappear also after the injection of saline solution alone. Seven of the cases which he treated were of moderate severity and 6 were light cases. None died. Of 10 severe cases, 1 died; while of 19 very difficult cases 9 died, a mortality of 47.3 per cent, as compared with a mortality of 75 per cent among such cases which received other treatment.

Stühlern has reported upon the treatment of 94 cases in three hospitals in St. Perersburg which were treated with Salimbeni's serum, of which 59 died, a mortality of 62 per cent. Other observers also thought the serum was of little value.

In regard to the serum produced by Kraus, reports have been made by Jegunoff. He used doses up to 140 c.c. with 500 to 700 c.c. of saline solution injected intravenously. Twelve patients were treated in this way with a mortality of 25 per cent, as compared with a general mortality of 75 per cent in cases which received no serum. In the cases in which no improvement resulted after the first injection, the second injection of from 80 to 120 c.c. seemed of no benefit. In cases in which the patient after the first injection escaped the algid stage, but which later showed anuria for two or three days, also the repeated injection of 80 to 120 c.c. did not prevent the development of parenchymatous nephritis, nor a fatal result. The number of cases treated is too small to draw any conclusions.

Hundögger treated 35 cases with Kraus' serum in doses of 100 c.c. mixed with 2 liters of sodium chlorid solution and injected intravenously. In some cases 100 c.c. was given intravenously, 50 subcutaneously, and 50 by mouth, in all about 200 c.c. The mortality was not reduced by the serum. Moreover, it appeared to exercise no influence upon the course of the disease and did not prevent the development of uremia.

A number of other observers have also failed to see any favorable action of the serum of Kraus upon the course of the disease or upon the mortality. Albanus treated 54 cases in which the mortality was 57.5 per cent, as compared with a mortality of 84.3 per cent in untreated cases. Kraus himself has assumed a therapeutic value for his serum upon the basis of observations upon 119 cases that were treated by Ketscher and Kernig. Of the 70 cases treated subcutaneously about 58 per cent died; of the 35 cases treated intravenously by Kernig, 51.3 per cent died; of the 12 cases treated by Ketscher, 50 per cent died, as compared to a general mortality of the severe untreated cases of 69.4 and 50 per cent. Kraus recommends the intravenous injection of serum at the earliest possible time in doses of 60 c.c. with 100 c.c. of physiological salt solution.

With the serum prepared under Kolle's direction by Carrière and Tomarkin 7 cases have been treated, 3 very severe, 2 severe, and 2 moderately severe. Only 1 of the very severe cases died. The entire quantities of serum for the different cases varied between 80 and 120 c.c. Besides the serum there were also injected large quantities of sodium chlorid solution intravenously. An unfavorable effect of the serum or appearances of serum disease were not observed in any of the cases.

During the epidemic of cholera in the recent Balkan campaigns cholera serum was extensively employed for treatment, but it is difficult to determine its value from the reports that have been made, since it was usually employed at the same time with other well-recognized measures of efficacy. The serum was obtained from the Pasteur Institute in Paris, from Berne, Vienna, and Dresden, no difference in treatment being noted with the various samples. It was generally given intravenously, sometimes in saline solution, in doses varying from 10 to 100 c.c. The opinions regarding its efficacy were divided among the different Greek physicians. Some believed it to be of value, while others saw no good results from its use. In the Salonika Hospital the mortality of a series of very severe cases treated with the serum in 40 to 80 c.c. doses, according to Savas, was 55.7 per cent. Savas, however, considers that when the serum is given intravenously sufficiently early in the disease, and in combination with saline injections, it is apparently productive of good results in many cases.

From a consideration of these observations it will be seen that no one has reported a lower mortality in a series of cases treated with serum than has been obtained by treatment with intravenous injections of saline and alkaline solutions. The average mortality during severe cholera epidemics is usually from 50 to 60 per cent. In cases carefully treated symptomatically with saline and alkaline injections, this mortality may often be reduced to about 20 per cent.

GENERAL PROPHYLAXIS

Cholera infection is acquired by way of the mouth and alimentary canal, usually through drinking water and food, sometimes by contamination of the fingers and hands with infected material. Infected water supplies have frequently given rise to severe epidemics. Food also often plays an important part in epidemics, particularly uncooked fruits and vegetables, salads, especially lettuce, and milk infected through water containing the cholera spirillum. Kabeshima has shown that the cholera organism is capable of passing down into the intestine of fish living in cholera-infected water, and that the disinfection of such fish is difficult. Flies may also carry the infection from excreta to various foodstuffs. Soiled clothing may also be a source of infection, and in cholera hospitals the ice-chests containing ice and foodstuffs have sometimes been infected by the hands of attendants and nurses. Whether an individual after receiving the cholera spirillum in any of these ways into the alimentary tract develops an attack of cholera or not, or becomes a cholera carrier, depends upon the virulence and number of the ingested organisms, the natural or acquired immunity of the individual, and whether the conditions are such that the organisms are able to pass through the stomach to the intestine without being destroyed by the gastric juice. Very avirulent cultures of the cholera spirillum have been ingested by several individuals with no untoward effects.

The cholera spirillum causing Asiatic cholera is found in enormous numbers and in almost pure culture in the intestinal discharges during the stage of evacuation, and in the intestine at autopsy of those who have died of the disease. Usually it is not found elsewhere in the body, but in 20 to 30 per cent of the fatal cases in some epidemics it has been isolated from the gall-bladder.

The disease particularly follows the lines of human intercourse. It may follow infected watercourses and is frequently carried great distances by cholera carriers or by individuals more or less sick with cholera. During epidemics of cholera in different parts of the world, the proportion of healthy carriers discovered in infected districts has varied from 6 to 22 per cent, while in individuals who have had an attack of cholera the vibrio may persist after complete recovery in about one-third of the cases. In the summer of 1912 the quarantine authorities at the large seaports on our Atlantic coast examined about 34,000 specimens of bowel discharges from passengers and crews from cholera-infected ports. At the New York quarantine the cholera vibrio was isolated from 28 persons sick with the disease, and 27 healthy persons were found to be discharging vibriones in their feces. Seven cases of cholera were detected at other ports by the same method. There can be no doubt that the adoption of this measure kept cholera out of the country. Those coming from infected localities should be detained under observation for five days. Hehir has recently emphasized the difficulties in detecting cholera carriers in India. Usually the cholera spirillum disappears from the stools of cholera carriers within from ten to fourteen days; but in rare instances it has persisted longer, from fifty to sixty-nine days. The suggestion that the cholera spirilla may exist in a form non-agglutinable to cholera immune serum in the feces of individuals for long periods of time and then change to an agglutinable organism and give rise to an epidemic of the disease still remains unproved. Many substances have been tried by the mouth with the object of destroying the cholera spirillum in the case of carriers within the period that the spirillum becomes naturally disposed of, but so far only unsatisfactory results have been obtained. Vaccination also does not reduce the period of infectivity of the cholera carrier.

From this discussion of the subject it will be evident that, in countries where the disease is endemic or epidemic, all uncooked salads and vegetables should be avoided. Drinking water and milk should be sterilized. All exposed foodstuffs should be carefully screened and protected from flies. The cholera hospital, and particularly the morgue, should be screened and also kept free of flies. A campaign against these insects should be undertaken. Doctors, nurses, and attendants on cholera patients should use every precaution to prevent the spread of infection from the handling of patients and infected material. All evacuations of cholera patients should be disinfected and bed linen boiled or otherwise disinfected. Every effort should be made to detect promptly cases and cholera carriers and isolate them and disinfect their excreta. Five per cent cresol is particularly satisfactory for this purpose. Where the water supply can only be derived from wells, these should be carefully chlorinated and individual drinking water boiled. Latrines should also be screened and carefully disinfected each day. Protective inoculation is particularly advocated for doctors, nurses, and attendants during epidemics, as well as for troops in the field and for the general population in heavily infected districts.

THE SPECIFIC PROPHYLAXIS OF CHOLERA ASIATICA

Vaccination.—Santoliquido of the Office International d'Hygiene Publique has expressed the opinion that a yearly cholera vaccination may be considered sufficient for the establishment of immunity unless specially dangerous circumstances exist, and that in the latter case a single injection of the vaccine is sufficient for reinoculation. It is suggested that, in non-epidemic periods, the spring is the most advantageous time for cholera protective inoculation, since summer and autumn are apt to be the most dangerous seasons. Animals which have been vaccinated frequently show immunity at the end of a year. Papamarku, who recently studied the sera of 60 soldiers inoculated against cholera, demonstrated that in the great majority of the cases the bacteriolysins begin to disappear after from six to seven months. He does not, however, consider that their immunity against cholera has terminated at this time. Yatsutomi has also demonstrated during the past year that the immunity produced by anticholera vaccination lasts for at least a year, and he believes that such immunity is as powerful as that due to an attack of cholera. Other observers believe the vaccination should be repeated after six months.

Inoculation.—Three methods of protective inoculation, all of which have been demonstrated to be efficient, are to-day particularly recommended. The first prophylactic, originally described by Kolle, consists of a culture of the cholera spirillum grown on nutrient agar suspended in sodium chlorid solution 0.85 per cent, and killed by heating for one hour at 53°C.; the second, described by the writer, consists of a filtered suspension of the immunizing substances, in normal saline solution, which have been extracted and digested from the cholera spirillum; and the third, particularly advocated by Besredka, consists of a sensitized vaccine obtained by shaking the cholera spirillum with cholera immune serum. The first of these prophylactics has the advantage that it is much more easily prepared, and the disadvantage that it may give rise to considerable local reaction, and that at least two inoculations are necessary to produce a satisfactory immunity. The second form of prophylactic is much more difficult to prepare but has the advantage that a larger amount of the immunizing substances may be given at a single time than it is possible to give when the killed organisms are employed, even though they are sensitized. A single inoculation is sufficient to produce immunity and there is practically no local reaction. The third prophylactic is also more difficult to prepare than the first, and there is diminished antigenic power as compared with the first two prophylactics. The local reaction, however, is less with this sensitized vaccine than in the case of the first prophylactic in which the entire cholera organism is also injected. Besredka has recently pointed out that, as anticholera immunity is essentially local, that is, in the intestinal wall, it would be more rational to give the vaccine by the mouth. Masaki has found, however, that the ingestion of living or dead vibriones by guinea pigs and rabbits is not followed by the appearance of antibodies. Only when living vibriones are given in enormous numbers by the mouth to rabbits and after the animals have first been sensitized by bile are antibodies formed. During the epidemic of cholera in Russia in 1922, immunization with killed cholera spirilla given by mouth was tried on a large scale by Zabolotny. Doses of from 10 to 20 c.c. of vaccine, corresponding in weight to from 0.05 to 0.10 gm. of dried bacteria, were borne without any reaction. In the serum of some of the persons thus treated, an increase in the titer of the agglutinating and bactericidal power of the serum was noted.

The numerous statistics concerning protective inoculation or vaccination against cholera which have been published from time to time would appear to prove conclusively the value of this procedure as an aid in the prevention of the disease. Statistics collected in India in earlier years seem to show that the number of cases among the inoculated was about one-tenth that observed in the uninoculated. In the Philippine Islands the statistics compiled through several years show that the proportion has been one-sixth the number of cases in the inoculated as compared with cases in the uninoculated. Important statistics have also been obtained in Japan. Thus, during the epidemic of 1902, 77,907 persons were inoculated. Of these, 47 or 0.06 per cent developed cholera, and 20 or 0.02 per cent died. Whereas, among 825,287 persons not inoculated, 1,152 or 0.13 per cent took the disease, and 863 or 0.1 per cent died. In 1904, in Japan, Murata reported that out of 10,000 inoculated 6 became sick, with a mortality of 42 per cent, while out of 10,000 uninoculated, 13 became sick with a mortality of 75 per cent. In 1917, Yabe reported that 301,224 persons were vaccinated out of the total population of Tokio and the suburbs of 3,055,946, or 10 per cent; of these, 3 who had not received full treatment sickened and 2 died. The records cover the non-vaccinated population of Tokio proper and include 2,661,767 people. Among these there were 680 cases of cholera and 442 deaths. In all the injections, not a single dangerous symptom was noted. During the recent epidemics of cholera in the Dutch East Indies protective inoculation was also shown to be of considerable value. Thus, of 15,368 natives inoculated only 2 developed the disease, 1 of whom died, while of 772 natives in the same locality not inoculated, 74 died of cholera or 9.6 per cent. Among the European population of Batavia, 8,000 were vaccinated, among whom 3 cases of cholera occurred, while, among 2,700 unvaccinated, 32 cases occurred with 15 deaths.

Arnaud has given the statistics on protective inoculation against cholera in the Greek army during the recent Balkan War. There were inoculated 93,868 men and 14,332 remained uninoculated. Of the inoculated 72,652 received two inoculations and 21,216 received one. In those inoculated once the incidence of cholera was 3.12 per cent; in those inoculated twice, 0.43 per cent; while in the uninoculated the incidence was 5.75 per cent.

Ottolenghi reports the vaccination with two inoculations of 72,653 soldiers, the incidence of cholera being about thirteen times less among them than among 14,332 who were not vaccinated.

Roy, in 1919, pointed out that vaccination against cholera had proved to be so highly efficacious in the army and labor corps in India as to warrant its extensive use as a prophylactic measure amongst the civil population during an epidemic. He believes he was able to check a recent epidemic of cholera in India by vaccination when other measures failed. The attacks in his vaccinated cases were 3.5 and in the non-vaccinated 16.5 per cent. Szyfman, during the epidemic of 1921 in Warsaw, also believed that anticholera vaccination helped to exterminate the epidemic. The statistics published by Young in 1919 show that among 106,934 uninoculated, and 89,609 inoculated, the ratio of deaths in the former was 6.78 and in the latter 1.8 per cent. In the recent Great War, the beneficial effects of prophylactic inoculation were also demonstrated by the statistics of Hoffmann for the German army and by Kaup for the Austro-Hungarian army. The statistics from Indo-China for the preceding year have also demonstrated the efficacy of anticholera inoculation, particularly among the troops which live side by side with the civil population.

Fejes has called attention to the fact that, in the case of those who contract cholera but who have previously received protective inoculation, the loss of fluid from the body is much the same as in the uninoculated, but the nervous symptoms in the case of the inoculated are much less marked, the toxins apparently being prevented from reaching to the same extent the portions of the body more distant than the intestine.

Vaccine Treatment.—Owing to the extremely acute nature of Asiatic cholera, vaccine treatment is of no value. The most acute symptoms of intoxication occur within from a few hours to two or three days of the onset of the disease, and immune bodies following protective inoculation are obviously not produced in large amounts during this period. In fact, the literature of cholera during recent years apparently contains only one reference in regard to the efficacy of vaccination in the treatment of this disease. In this instance concerning an epidemic reported by Petrovich in 1914, the mild cases (1,153) were given small doses of cholera vaccine daily until the diarrhea ceased. Cases of medium intensity (90) were given the cholera vaccine in normal serum (from 10 to 100 c.c. intravenously, sometimes as often as twice or thrice a day. Severe cases (157) were treated like those of medium intensity but received the vaccine in 500 c.c. of saline solution. Under this method of treatment the author states that all the cases of medium intensity recovered and the mortality in the severe cases was reduced to 14.4 per cent in contrast to a mortality of 58 per cent for 120 severe cases not given vaccine treatment. These conclusions are unconvincing and have apparently not been repeated or confirmed.

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INFECTIONS DUE TO COCCI

CHAPTER XXVIII

SEPTICOPYEMIA

George Dock

Definition.—The word septicopyemia is a convenient one by which to designate certain forms of infection still incompletely known, or at least impossible thoroughly to understand during the life of the patient. It replaces with advantage some terms that came into use before the details of infection were as well known as they now are, but it is in truth a collective word, and is as objectionable as "fever" or "dropsy," but on account of the practical difficulties of exact microbic diagnosis it may be used until the various infections that now enter into it can be distinguished, as we now distinguish typhoid and recurrent fevers. It replaces, especially, two older words that came into use before accurate ideas on the subject were possible, and that are still used rather loosely, but without realizing the latter fact.

"Septicemia" is applied to conditions in which there is microbic invasion, usually bacterial, of the blood and tissues, without foci of suppuration. It is more comprehensive than "bacteriemia," which appeals to many as more precise.

"Pyemia" is an old term now used in the sense of an infection with a pus focus, with intoxication—still spoken of as "toxemia"—from the poisonous substances formed by or from the germs in the focus, or from the tissues affected by the germs or their products. It is still a part of the conception of pyemia that metastatic foci may be set up by the action of germs carried from the primary focus. It is obvious that the differentiation of such cases from cases of septicemia depends upon methods that are useful only when positive. Negative results often depend chiefly upon imperfect search. The source of a septicemia may be known, and its character determined by the examination of material from the source, as in puerperal disease.

On the other hand, the local disease may be due to one germ, the general disease to a different one, as we see in staphylococcus infection originating in gonorrhea, or a streptococcus septicemia that has entered through a staphylococcus skin infection.

In many cases of septicemia and septicopyemia there is no discoverable local lesion during life. To such the term "cryptogenetic" is applied. In many cases no primary focus can be found in the most careful search postmortem, either because the primary focus or portal of entry has healed, or because there was no portal in the sense of a gross solution of continuity, the germs having entered through the skin or mucosa and having found unusually favorable conditions for growth.

Etiology.—The causes of septicopyemia are numerous. The most important are streptococci, staphylococci, pneumococci, including the nearly related Micrococcus viridans, colon bacilli, influenza bacilli, proteus, pyocyaneus, and anthrax, but other germs, such as typhoid bacilli, Micrococcus tetragenus and Friedländer's bacillus, may be concerned.

From the list given it is clear that the practitioner should always attempt the exact diagnosis, just as he now aims to distinguish between typhoid fever and miliary tuberculosis. That he does not depends not so much upon force of habit, which has made the idea of septicemia as satisfactory to many as that of typhoid, as it does upon the practical difficulties in the exact diagnosis. Another reason is that the treatment of such disease must necessarily be upon a rather general basis. But even if the efforts at specific treatment have so far been disappointing, it will only be after we are able to distinguish each form of infection that we can draw accurate conclusions as to the result of treatment in actual cases.

Pathology.—The pathologic anatomy involves the specific lesions, if the germ is one that can produce such; or there may be a primary focus, as said before, which may be very minute. From this focus bacteria may be swept out or get into the lymph or blood circulation, and by their presence or by their poisons, absorbed from them, produce other lesions or symptoms. We know little about the entrance of germs into the circulation, but we know that in some cases such invasions are very irregular in time and number of germs set free. The toxic effects may be so slight as to be unnoticed; or so severe as to cause the most striking clinical phenomena.

Among the local lesions, next to suppuration, thrombosis and embolism are most important features. The thrombosis usually originates in an infectious phlebitis or arteritis. No satisfactory reason can be given for the fact that in some cases suppuration is severe, in others there is phlebitis or endocarditis, in others none of them, but marked growth of bacteria in the vessels, especially in the capillaries.

Symptoms.—The symptoms of septicopyemia are of great diversity and of all degrees of severity. Chills, fever, sweating, especially intermittent fever with great excursions, sometimes as much as 8° or 10° F., within a few hours, collapse temperature and cardiac arhythmia, are perhaps the most striking. Malaria is still too often suspected, and still other so-called tropical diseases, such as Malta fever. Enlargement of the spleen is almost the rule in septicopyemia. Sometimes sudden pain and tenderness in the splenic region permit the diagnosis of infarct, which may lead to more accurate diagnosis than was possible before. Weakness, headache, anorexia, malaise, emaciation, sallow or subicteroid complexion may be the chief features in another class. Besides headache, dizziness, insomnia, convulsions, delirium, and coma occur, especially when there is thrombosis or embolism or suppuration within the cranium. Retinal hemorrhages also occur. Leukocytosis is a frequent sign, but in some cases there is the blood picture of a primary anemia without leukocytosis. Joint pains and arthritis of all varieties are the characteristics of others; osteomyelitis is always to be looked for. Petechiæ, or larger skin hemorrhages, hematuria, or blood spitting are sometimes the clues to the existence of septicemia.

Endocarditis is a frequent accompaniment of septicopyemia. Many cases diagnosed as the former are really cases of septicemia or septicopyemia, in which the heart shows conspicuous symptoms; enlargement of dulness, weak muscular sounds, murmurs, and irregular rhythm are usually present. Very often the enlargement of the heart is slight, either on account of the lesion being mitral stenosis, or because of the fact that from the feeling of weakness and tendency to high fever the heart is spared the exertion that would otherwise cause enlargement.

Diagnosis.—The diagnosis may be made in many cases by a carefully taken history, with temperature record, and accurate physical examination, including that of the blood. Exclusion of diseases that might cause a similar picture is an essential part of the work. The most important single diseases to differentiate are acute arthritis of rheumatic type, malaria, typhoid fever, and miliary tuberculosis; next to these other acute infectious diseases, only necessary to consider in the early stages; later, with emaciation and anemia, chronic blood and constitutional diseases must be excluded.

The diagnosis should always be completed by blood cultures, and cultures from any suppurative foci that may be found. As this is work that can only be done by experts, it is not necessary to go into details. In order to make the findings of scientific value the most exact differentiation of germs must be made, as in the case of germs of the colon, diplococcus and streptococcus groups.

Prognosis.—The prognosis depends partly upon the nature of the germ, partly upon the severity of the infection, the previous health and resistance of the body, and the ability of the patient to secure proper treatment.

Bodily resistance cannot always be estimated, but we know that the old, the drunkard, the diabetic, the cachectic, and the arteriosclerotic react badly to all infections.

Streptococci usually give a bad prognosis. Recoveries have been reported from all forms, so that an absolutely hopeless prognosis should not be made merely upon the discovery of a septicopyemia.

If a local lesion susceptible of surgical treatment can be found, the prospects are often better than in purely cryptogenetic cases.

The duration of the disease before the discovery has an important bearing upon the prognosis. Many cases of pyemia from various causes are amenable in the beginning, but almost wholly intractable after septicemia is well developed. Colon bacillus infections are especially difficult to eradicate when of long standing, as compared with their early stages.

TREATMENT

Prophylactic Treatment.—Prophylactic treatment of septicopyemia is one of the chief aims of Listerian surgery. This is probably not realized as universally as it should be, and numerous cases of local infection in the skin, bones, and peritoneum, gastro-intestinal and genito-urinary tract, ears, and other organs are permitted to go on unchecked. The fact that many cases never cause serious trouble explains the common neglect, but cases of malignant endocarditis, of brain abscess and of general sepsis develop out of them often enough to show, as in other diseases, that none can safely be considered trifling.

Surgical Treatment.—Surgical details need not be described here. Radical healing, as early as possible, is the aim.

Specific Treatment.—Specific treatment should be experimented with in various ways until the possibilities are exhausted. Even medicinal assistance for this object must not be abandoned. The early objection to such efforts—that it is impossible to use antiseptics that will not be more dangerous to the host than to the germs—is based upon an imperfect knowledge of the facts, though true in general. We know that different kinds of organisms show different degrees of sensibility to various poisons. The treatment of intestinal animal parasites illustrates this. The field, so far from being exhausted, has only been touched. New preparations are sure to be invented that will have peculiar advantages and minimal disadvantages. Such preparations as colloidal silver salts, urotropin, and salicylates have brought disappointment to many, but in the results of their use we can find numerous suggestions for further trials, carefully observed and accurately controlled. It does not seem necessary to lay down rules for the administration of any of these preparations, but one general rule should be emphasized: that they must be used early, and not deferred until the body is overwhelmed with infectious material. Another feature in the use of these and other similar substances is the importance of intravenous medication, as well as the more definite trial of intramuscular injections.

The use of sera and vaccines has been disappointing in many forms of sepsis, and the differences of action of some of these infections, as compared with that of diphtheria and tetanus, have made many deny the possibility of future improvement. This may be the final verdict, but it is too early to abandon further investigation, and all methods that appear promising from experiments on animals should be followed up in appropriate human subjects.

Owing to the experimental character of the treatment and the fact that it should only be used where complete bacteriologic examinations are being carried on, with such other examinations as are indicated—opsonin determinations, hemolysis tests, complement fixation, etc.—details must be worked out in each case. In practice, even with the most careful examinations, trials may be made of various preparations besides those of the germs cultivated, but without such cultures and all the other work the treatment cannot be considered any better than the crudest empiricism.

Symptomatic Treatment.—The symptomatic treatment offers many details of importance. The possible dangers from exertion must be avoided by proper nursing. Fresh air treatment is often of decided advantage, and patients with severe symptoms should be in the open air, with all the necessary details. On general principles, as well as on account of the danger from imperfect excretion of waste products in cases of infection, the alimentary canal should be unloaded early and retention prevented by the use of enemata or colonic flushing at intervals. The function of the kidneys should be carefully observed, and stimulated by a sufficient amount of water regularly. Although the early hopes of tissue irrigation have been disappointing, the systematic use of physiologic saline solutions has advantages in washing out toxins and in keeping up the vascular and cardiac tone. The slow proctoclysis, as improved by Murphy, is the best way of using salt solution, giving 500 to 1,000 c.c. from one to three times a day.

The food should be simple, easily digestible, and supporting. Eggs and milk are usually the chief elements of the diet. Broths, gruels, purées, and fruit juices, arrowroot and cornstarch preparations, and fruit jellies are useful aids. Tea, coffee, and milk or cocoa serve as stimulating beverages.

The question of the value of alcohol in septicemia is still unsettled. As a routine, I have for many years wholly excluded it in the treatment of all infections, and I have not been able to recognize any loss as compared with other cases treated formerly by myself, or now by other physicians. Perhaps as a substitute for food or as a psychic pseudostimulant it may be useful at times, but I believe that hot drinks, hot saline enemata, ice-bags to the precordium, or the cold, full bath are more useful general stimulants.

Certain other remedies may be used for vasomotor or cardiac weakness. Among these are caffein or strong coffee, strychnin, digitalis, and camphor, the latter hypodermically in the form of camphorated oil.[1]

The gastric irritability of sepsis should be treated with cathartics and diet. The diarrhea, which may be an important, even vital, factor, should be treated by cathartics, such as calomel or castor oil, colonic flushing, and such remedies as salol, bismuth, and betanaphthol.

Pain should be treated with analgesics like aspirin, phenacetin, or morphin, according to the indications. Efforts should be made to secure sleep by the use of veronal, trional, bromids, and morphin.

Delirium calls for the ice-bag and hyoscin hydrobromate.

Organic diseases like pneumonia must be treated as under other conditions.

The danger of heart and vasomotor weakness must always be borne in mind. Even late in convalescence no sudden or prolonged exertion should be permitted. If there is endocarditis, the precaution must be most minute.

If anemia is severe, transfusion of blood is necessary. Even in cases with hemoglobin of 70 per cent or more, transfusion of 400 or 500 c.c. often seems to stimulate recovery.

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[1] Also adrenalin.—Editor.

CHAPTER XXIX

THE PNEUMONIAS

Henry L. Elsner, Henry T. Chickering, Rufus I. Cole,
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GENERAL TREATMENT

Henry L. Elsner

Revised by Henry T. Chickering

Pneumonia is a systemic infection usually associated with febrile disturbances in which large portions of one or both lungs are involved in an inflammation, due, as a rule, to the pneumococcus of Sternberg and Fraenkel, though it may be associated with a variety of other bacteria. Bacteremia, toxemia, pulmonary consolidation with consecutive obstruction, and respiratory asthenia form the complex which demands attention in the average case.

The clinical classification of cases with lobar or lobular inflammation of the lungs has in the past been mainly based upon the anatomical lesions. While such a classification is of importance, as the possibilities of specific therapy become greater the need for a classification of the cases upon an etiological basis and the diagnosis of each case from this standpoint becomes increasingly great. The work of Neufeld in Germany and of Dochez and Gillespie and others at the Hospital of the Rockefeller Institute has demonstrated that the pneumococci differ in their immunological characteristics, and that upon such immunological features they may be divided into several groups. The mortality in cases due to organisms of these various groups differs, and therefore the diagnosis of etiology in each individual case becomes of considerable importance, not only from the standpoint of therapy, but of prognosis as well.

Typical lobar pneumonia characterized by a chill at onset, blood-tinged tenacious sputum and massive consolidation of one or more lobes of the lung is associated with the pneumococcus in about 97 per cent of all cases.

The Friedlander pneumobacillus usually produces an extensive lobar type of pulmonary lesion but is an extremely rare etiological agent.

There were only 3 in Cole's series of 529 cases of pneumonia at the Rockefeller Hospital.

Many mild atypical cases of pneumonia, which would be classified as bronchopneumonia on the basis of physical examination of the lungs, are associated with the pneumococcus. There are, however, many cases of atypical pneumonia, clinically bronchopneumonia, which are apparently caused by B. influenzæ, Streptococcus hemolyticus, Streptococcus viridans, Staphylococcus aureus, B. typhosus, and tubercle bacillus.

Table I shows the variation in the mortality in a group of cases of lobar pneumonia associated with the various types of pneumococcus.

Mortality Variations of Different Types

Type	Cases	Deaths	Death-rate Per Cent
I	175	41	23.4
II	206	62	30.1
IIa	58	13	22.4
III	97	44	45.4
IV	205	32	15.6

The Type I and Type II pneumococcus are responsible for about 55 to 60 per cent of cases of lobar pneumonia seen in the United States. The mortality ranges from 20 to 30 per cent for adult hospital cases. Patients seen in private practice and treated wisely from the onset of the disease undoubtedly show a lower mortality as did many of the army series. The Type III pneumococcus in about half the cases seen produces a very virulent and rapidly fatal infection. Curiously enough the other 50 per cent to 55 per cent may exhibit a relatively mild course. Fortunately this group makes up only about 10 to 12 per cent of the cases. The Type IV pneumococcus, responsible for about 25 per cent of the cases, produces a relatively mild lobar pneumonia.

It is the Type IV pneumococcus that is seen so commonly in the bronchopneumonias and it is likewise the type of pneumococcus found most frequently in the nose and throat of normal individuals.

It seems quite probable that factors that materially reduce a person's vitality, as antecedent infection, influenza, measles, malnutrition, general anesthesia, old age, may render this ordinarily harmless saprophyte a disease-producing organism.

Table II shows the various organisms associated with three groups of secondary pneumonias which were largely bronchopneumonia from a clinical classification.

Olmstead's cases were determined by sputum examinations. Wollstein's and Chickering's and Park's series were postmortem lung cultures.

In all three groups the very low incidence of the Type I and II pneumococcus infections, which make up the majority of the true lobar pneumonias, will be noted.

TABLE II—BACTERIA ASSOCIATED WITH SECONDARY PNEUMONIAS

Organism	Olmstead	Wollstein	Influenza Pneumonia
Pneumococcus Type	Postoperative Pneumonia 126 Cases Sputum Cultures	Infant Bronchopneumonia 103 Cases Postmortem Cultures	Postmortem Lung Punctures 312 Cases
I	1	2	6
II	1	2	16
IIa	8		
III	12		29
IV	73	18	41
Pneumococcus, type undetermined		10	2
Pn. I and Streptococcus hem.			1
Pn. I and B. influenzæ			1
Pn. II and Staphylococcus aureus			5
Pn. II and B. inf.		1	3
Pn. II and B. inf. and Staph. aur.			1
Pn. II and Strep.		1	
Pn. III and Staph. aur.			4
Pn. III and Staph. aur. and B. inf.			1
Pn. III and B. inf.			7
Pn. IV and Staph. aur.		1	16
Pn. IV and Staph. aur. and B. inf.			1
Pn. IV and B. inf.		1	2
Pn. IV and B. Diphtheroid			1
Pn. IV and M. Flavus			1
Pn. and Staph. aur.		11	
Pn. and B. tubercle		7	
Pn. and Strep.		10	
Pn. and Klebs-Löffler B.		1	
Pn. and B. pyocyaneus		2	
Pn. and B. coli		2	
Staph. aur.		6	92
Staph. aur. and B. inf.			17
Staph. aur. and Strep. non-hem.		3	3
Staph. aur. and Strep. hem.			5
Staph. aur. and Strep. vir.			2
Staph. aur. and misc. organisms			4
B. Inf.	1		19
B. Inf. and Strep.			4
Strep. hem.	9		6
Strep. non-hem.		6	7
Strep. and misc. organisms	1	6	4
B. mucosus capsulatus	9		
Misc. organisms		3	5

Prognosis.—The mortality from bronchopneumonic infection varies widely, from practically zero to an extremely high figure, depending on the previous condition of the patient and the infecting organism. The postoperative pneumonias are usually associated with a very low mortality. With the pneumonic complications following measles and influenza in adults the mortality is high.

The bronchopneumonia associated with the Type IV pneumococcus, other factors being equal, offers a much better prognosis than those associated with the hemolytic streptococcus or Staphylococcus aureus.

A pure influenza bronchopneumonia, while not usually fatal, quite frequently runs a protracted course, there being an irregular fever for several weeks.

With the pneumococcus pneumonias it is infrequent to find a purulent pleural fluid before the tenth to the fourteenth day, while with the hemolytic streptococcus infections one pleural cavity may be filled with amber-colored cloudy fluid containing streptococci as early as the second or third day.

The knowledge that one is treating a hemolytic streptococcus infection, therefore, may be of utmost importance. It is frequently difficult to determine from physical signs alone whether one is dealing with a massive pneumonic consolidation or a pleural cavity filled with fluid. Here one is quite justified in exploring the chest with the needle even early in the disease. For if fluid is present, repeated early tapping may effect great relief to the embarrassed respiration.

On the other hand if one is treating an early pneumococcus infection one is much more inclined to proceed conservatively as regards exploration of the chest.

Another characteristic of streptococcus infection is the early development of multiple pockets of purulent fluid in the chest. The tapping of one pocket may produce no relief and the clinician must search for other hidden accumulations of pus. Hemolytic streptococcus infections are much more prone to develop pockets in the anterior portions of the chest than the pneumococcus, though I have seen a few pneumococcus infections in which pus was obtained only by exploration anterior to the anterior axillary line.

Consequently it is highly important that an earnest effort be made in every case of respiratory infection to determine the etiological agent. With adults it is not usually very difficult to obtain a specimen of sputum from the deeper air passages. With young children and some women it may be more difficult. On the first examination if the physician will have a sterile Petri dish at the bedside, the patient usually can be made to produce a specimen of sputum. If sputum cannot be obtained at once, the Petri dish should be left at the bedside with instructions to the family to bring the specimen as soon as produced to the physician's office or designated laboratory.

With appropriate bacteriological methods the predominating organism can be determined and the type of pneumococcus if present.

The pneumococcus can best be recovered from the sputum and its type determined by injecting a small amount of the specimen into the peritoneal cavity of a white mouse.[1] A platinum loopful of the sputum should be streaked over the surface of a blood agar plate in order to determine the predominating organism. All the various organisms found in pneumonic sputum grow readily on this culture medium.

If the mouse method alone is relied upon, when one has a hemolytic streptococcus infection to deal with, there may be too few organisms or their virulence may not be sufficient to kill the mouse. Consequently the predominating organism would remain unknown.

It is also important to stain smears of the sputum for tubercle bacilli, for in large series of cases tubercle bacilli are found in about 1 per cent of cases of lobar pneumonia. Their presence naturally has a decided effect on the prognosis of the individual case.

The lobar pneumonia of typical onset and signs is usually a simple diagnosis. There are unfortunately many cases of respiratory infections, especially as seen in private practice, that are more difficult. The majority no doubt are well in a few days, in other words an upper respiratory infection. However, if the deeper air passages are involved, one symptom is quite common, and that is loss of appetite. The patient suffering from coryza, tracheitis, or bronchitis, with or without fever, usually has a good appetite. The potential pneumonic rarely does. If in addition there are a few fine râles confined to one side of the chest, the anorexia is even more significant.

These cases are frequently ambulatory for several days before the diagnosis is made and often subsequently exhibit virulent and fatal infections.

I have seen a few patients who with the initial chill expectorated a small amount of tenacious blood-tinged sputum. Upon cultivation on blood agar plates and passage through white mice, pneumococcus Type III was obtained. It is this organism that produces a 45 per cent mortality in hospital cases. In two cases, only a small patch of localized râles was found and the temperature was normal in three days. But the patient, though apparently never ill, was not allowed up for two weeks. Would the physician treat his patient thus if he were not sure that an organism producing a 45 per cent mortality was lurking in the deeper parts of the lung? The determination of the infecting agent is just as important as the medicinal treatment. It is often the indication for treatment.

If the physician can command the facilities for the taking of blood cultures, this procedure should be employed in every case of definite lobar or bronchopneumonia. It checks up the results of sputum cultures and it is a definite aid in the prognosis. In Cole's series the mortality in those having negative blood cultures was 11.6 per cent in 343 cases, while it was 67.1 per cent in 119 cases having positive blood cultures.

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[1] For the details of this method see Monograph No. 7, The Rockefeller Institute.

EPIDEMIOLOGY

The studies of Dochez and Avery, Stillman, and Blake and Cecil, leave very little reason to doubt that contact with the disease-producing types of pneumococcus, Types I and II, is a major factor in the spread of pneumonia. This, however, does not explain why so few of those exposed to infection develop the disease.

Although little is accurately known concerning either natural or acquired immunity in man to respiratory infections, it is quite certain that marked differences in susceptibility exist.

Physical exhaustion, unusual exposure to the elements, or sudden changes in habits of living or trauma increase the susceptibility to infection.

A rather striking instance of the coöperation of some of these factors in the production of a "take" may be noted. After eight years of intensive exposure to pneumococcus infections, the writer had occasion to treat a very virulent atypical Type II pneumococcus infection. This patient clinically had the physical signs of an influenza bronchopneumonia. A harassing cough which resisted all forms of medication was present.

After an exposure of about two weeks, the writer developed a mild bronchopneumonia of the same type. As this type of pneumococcus is relatively uncommon, the inference may be fairly made that it was a contact infection. A preceding period of unusual fatigue was the only obvious factor that indicated lowered resistance, while the excessive coughing offered unusual exposure.

The influence of sudden changes in environment and occupation is illustrated by the high incidence of pneumonia formerly among the new native workers in the South African diamond mines, and among the new recruits in our own army during the war as contrasted with that among the seasoned workers or soldiers.

The history of primary lobar pneumonias shows mild upper respiratory tract infections to have been present in about 50 per cent of the cases.

Measles and influenza especially increase the susceptibility to pneumonia, as do general anesthesia, prolonged operations, malnutrition and other debilitating diseases.

PROPHYLAXIS

With the increasing knowledge of the many factors that render one more susceptible to the pneumonias it is highly important to keep in as excellent physical condition as possible. Persistent fatigue and lassitude are danger signals. Undue exposure should be avoided.

Mild respiratory infections should be treated as potentially serious. Imperfect ventilation of the nose and faulty drainage of the accessory sinuses of the nose and chronic infections of the tonsils and nasopharynx should be carefully treated.

Patients suffering from measles and influenza should be kept in bed for several days after the fever has disappeared and then be allowed up only very gradually.

To prevent the direct transference of the infecting organism, close contact with the patient must be avoided. Physicians and attendants, and especially relatives, should wear masks in the sick room for the moral effect—that is, to show that in contact there is danger.

It should be remembered that it is possible to inoculate blood agar plates with pneumococcus when held ten feet from the patient's mouth when vigorous coughing is taking place.

All sputum would be collected on small pieces of cut gauze or paper napkins and deposited in a paper bag pinned to the bedside, which is then burned with its contents.

If the patient is delirious and expectorating promiscuously a draw sheet should be stretched across the bed beneath the patient's chin and be changed when contaminated.

After bathing or any contact with the patient, the nurse should carefully wash and disinfect her hands. All dishes used by the patient should be boiled.

Oral Cleanliness.—Oral cleanliness is exceedingly important at all times and in all individuals. False teeth and partial plates should be removed from the mouth during the acute stages of the illness. If there is any local inflammation or exudate in the mouth and throat, hot irrigations of a solution of bicarbonate of soda, one teaspoonful of bicarbonate of soda to one quart of hot water, give great relief.

A very valuable and efficacious mouth wash which the author has used with satisfaction is the following:

℞	gm.	
Creosoti	0.6	(grs. x)
Tinct. myrrhæ	10.	(ʒiiss)
Sodii bicarbonatis	8.	(ʒii)
Glycerini	32.	(℥j)
Aquæ Menth. piper. ad.	240.	(℥viii)

Nurses and Attendants.—Nurses and attendants should protect themselves while in service by the frequent use of nasal and mouth washes, and should maintain their health at par by getting sufficient sleep, fresh air, and plain but sustaining food.

Public Health.—The state owes the individual a duty, which includes the scientific *ventilation of public buildings,* schools particularly, and the cleaning of streets and pavements in a way which will reduce the dust nuisance to a minimum.

Correction of Predisposing Conditions.—*Abnormalities and obstructions* should be removed from the air passages of children. The masses should be educated to an understanding of the influences of *alcoholic excesses* and dissipation in inviting infection of all kinds, particularly pneumonia. Supposedly *trivial ailments of the respiratory tract,* particularly the fauces, and the alimentary canal should be treated with a view of preventing possible graver pulmonary complications.

Carriers.—The pneumonic should be instructed during his convalescence that the infecting agents may find a resting place in his air passages during an indefinite period after relief from symptoms, and that he may be an active "carrier" of the infecting microörganism.

Disinfection.—All linen and clothing coming in contact with the patient should be thoroughly disinfected by boiling. The room after the termination of the disease should be subjected to thorough cleansing and fumigation.

Prevention of Secondary Pneumonia.—Forchheimer wisely calls attention to the prevention of secondary pneumonia following other infections, particularly during convalescence, by all possible precautions.

Ether pneumonia is in all probability a preventable disease. All who are subjected to ether anesthesia should, if the stomach is not known to be empty, be thoroughly lavaged, certainly if the operation is to be long or upon the intestinal tract. Mouth and nasal passages should be cleaned before the administration of the anesthetic. The inhaler that is employed should be sterilized each time before it is used.

The possible prevention of complications in the pneumonic, based upon the action of *hexamethylenamin,* has led to its administration. Some claim that empyema, pericarditis, endocarditis, and otitis media have been prevented by its routine use. In the Massachusetts General of Boston and Presbyterian Hospital of New York results have been favorable in connection with the occurrence of pericarditis in those taking the drug. Cases not taking the drug developed the complication in 4 to 5 per cent at the Massachusetts General, and 1.5 per cent at the Presbyterian Hospital. The Massachusetts records show that otitis media occurs in 4 per cent of the non-hexamethylenamin cases; in no instance in which the drug was administered.

Cleanliness.—Hands should be kept clean; children as well as adults should keep money and unclean objects out of their mouths.

Education.—Positive and printed directions, which will make clear the nature and dangers of infection and the methods of its prevention, should be given the heads of all families. The *campaign of education* which is being waged will ultimately reap reward which it deserves.

TREATMENT

General Treatment

An intelligent *nurse* ready to make sacrifices, quiet and refined, with good poise, is as necessary as the intelligent physician in the care of the pneumonic. The patient should be provided with a suitable *bed* in the best ventilated room which the house or hospital affords, preferably one having sunshine. The bed should be thoroughly warm when the patient gets into it. The best bed for protracted illness of any kind is the plain single hospital bed, made sufficiently high, with a well-made mattress and stiff woven wire springs. The standard hospital bed is 6 feet 6 inches long, 36 inches wide, and 26 inches high; if necessary for the comfort of the attendants, this may be raised on blocks. It should stand, if possible, in the middle of the room; the sheets are to be smoothly laid and kept so; the protecting rubber and draw-sheet should not be omitted. *The patient should not be burdened by unnecessary covering.* He is laboring from the beginning of the disease to overcome mechanical obstruction in the lung, and is in no condition to lift unnecessary weight or coverings with each inspiration. Considering the rapidity of respirations, the importance of this fact at once becomes clear. Children are often made the victims of oversolicitous but deluded mothers and uneducated attendants by failure to appreciate the truth of these statements. *No pneumonic should be handicapped in his fight for air and light. All unnecessary furniture and trimmings should be removed from the room.* The temperature of the room should be from 60° to 65° F., rarely 68° F.; the aged and feeble and very young may require the latter degree of heat.

Open-air Treatment.—If the patient is in the *open air* it does not matter how low the temperature, so long as his body is kept comfortably warm, his head covered, his respiratory organs free to breathe the unadulterated tonic air.

The open-air treatment of pneumonia is not an innovation. With increasing refinements of practice and the educating of the masses to the understanding that the modern therapeutist includes in his armamentarium nature's methods of curing disease, always natural and rational, and a lowered mortality, the public is ready to accept our conclusions and the individual has less fear of pure cold air. Every case of pneumonia, unless there are positive contra-indications, should be treated in the open air or in a room in which the supply is sufficient to meet the demands of his case. Forchheimer says, "I do not hesitate to affirm that the fresh-air treatment is the most valuable contribution that has been made for the treatment of pneumonia." The experienced are ready to verify the truth of Forchheimer's emphatic statement.

Modern hospitals are built to supply the need of infection requiring the open-air treatment. Most hospitals have either a room or a ward which can be easily transformed to meet the needs of the pneumonic, while the home, however humble, has a room or space which will permit of the treatment either by improvising the window tent, easily accomplished, the removal of window sash, or such other modifications of the surroundings as are necessary.

If the patient is treated in the open air, it is quite important that arrangements be made so that the bed can be moved into a warm place when the patient is examined, the bed clothing changed, or for any reason exposure is necessary. Every effort should be made to keep the patient's body warm, and it is important to remember that not only is covering necessary, but also sufficient blankets to cover the mattress should be provided, in order that the heat may not be lost by radiation downward. An important point to be remembered in outdoor care of patients is that the nurses should be cautioned to wear sufficient clothing to guard against cold. It is not necessary to expose the nurse to undue risk in order to aid in the recovery of the patient.

Once the patient has been brought under the tonic and exhilarating effect of the pure, fresh air he is a convert, unless robbed of consciousness. By the giving of fresh air vitality is sustained or strengthened, the work of the heart is reduced, that organ gets more sleep because its periods of rest are prolonged, the patient breathes slower. The effects are promptly apparent, and, in many cases, even in alcoholics whom we have treated in our hospital services, the delirium was reduced, sleep was increased and restful. The influence on temperature is favorable, while the cough is lessened. Blood-pressure is heightened by exposure to the open air. At Bellevue Hospital (Meara) it has been noted that there was a rise of 10 to 20 mm. Hg promptly after removal to the open air, which was as promptly lost after a half hour in the ward, though the latter was well ventilated. The rise returned on return to the open air. It was further noted that the rise was more marked when the temperature of the inspired air was low. I have had similar experiences in my hospital service and private practice. *Less medicine is needed and Nature is assisted in her own effort to save life when the patient is in the open air.* The lower the temperature the greater is the tonic effect of the inspired air. Brannan, who, as trustee of four of the largest hospitals in New York City, speaks authoritatively on this subject, unreservedly approves it after a sufficient trial, and, after commending it for adult pneumonia, says: "I have often on my visits seen a dozen cribs on an open balcony on a bright cold winter's day and with not a sound coming from the children. It was an impressive contrast to the fretting and wailing of the ordinary infants' ward."

"Conditions exist outdoors that tend to a more rapid heat loss than indoors. The lower temperature of the outside increases humidity, and the greater amount of air movement gives us a more rapid loss of heat by all the methods—radiation, convection, and conduction—than inside, and on the face of things it seems to me this is the real differential effect the outside air has as compared with the inside air; that is, it increases the loss of heat, which in turn calls upon the organism to supply a greater amount of heat in order to keep up its body temperature, and this in some as yet occult way stimulates metabolism" (Phillips). Whatever the theory, we know that in practice the open-air treatment of pneumonia is rational and a valuable adjunct.

If the open-air treatment of pneumonia is practiced in cold weather, it is extremely important for the patient to be constantly watched to avoid direct exposure of the chest to the cold air. Pneumonia jackets made of gauze and cotton wadding should always be worn over the woolen gown. Intermittent temporary chilling of the body does more harm than the out-of-door treatment confers.

Diffuse bronchopneumonia seen as a complication of measles and influenza does not seem to be benefited by the open-air treatment. Here the ideal condition is an abundance of fresh moist air of about 60° to 65° F.

Position in Bed.—Position in bed is important. As a rule, it is best to turn the patient from side to side, but let him get into the position in which he breathes easiest, remembering always that hypostatic congestion must be discouraged. All patients suffering from pneumonia should be kept constantly in bed. Every form of exertion should be avoided. The patient should be assisted when turning in bed or when the bed-pan is used.

Most patients breathe easily in the horizontal position. With elderly individuals, it is wise to allow as many pillows as will insure the maximum ease to respirations. The semi-inclined position is usually more comfortable for the obese.

The *hearts* of pneumonics from the beginning to the end of the disease are taxed by any movement of the body or any of its parts, speaking or any effort; any increase of the heart's action unnecessarily provoked adds to the danger of the disease, and should be cautiously avoided. The pillows should not be too soft, for if they are the patient sinks into them and seeks to raise himself at short intervals. Because of this fault neither feather pillows nor such covers should be allowed. The hair pillow is preferable. Combination suits make examination difficult; the old-fashioned nightdress, thin, kept from wrinkling, is most comfortable, and makes it easy for the attendant to watch the abdomen and thorax without greatly disturbing the patient.

Examination of Patients.—The patient should be given a thorough physical examination on the first, second, and third days of the disease; the extent and location of the consolidation once cleared, it is useless and injurious to move the patient from side to side, or worse to raise him in bed for further examination. Most important is the thorough examination of the *heart and pulse,* as well as the extremities. The abdomen and bladder should be carefully examined for evidence of distention at each visit. If after the third and until the seventh day the posterior thoracic regions demand examination, the flat phonendoscope may be used, or, if necessary, the position may be changed by the "draw-sheet" without the patient's effort.

The *temperature of all pneumonics should be taken in the rectum!* Respiratory embarrassment is increased by the holding of the thermometer under the tongue; this is particularly true in the later stages of the disease. The raising of patients in hospitals for examination by medical students in sections is unnecessary and injurious! A single demonstration of percussion may be given by the teacher, after which the patient, remaining on his back, may be drawn to either side of the bed for mediate or intermediate auscultation, the study of voice sound, fremitus, etc. Judgment tempered with humanity on the part of the teacher and student will be needed to conserve the strength and resistance of these patients.

Care of Body.—The average case does not require tubbing or packs, but should be kept clean and comfortable by surface bathing with warm water, under covers, morning and night. If there is excessive perspiration, cloths dampened with alcohol may be used, then rough towels for surface friction, all without exposure of the patient. The use of carbolated talcum powder to all folds and often to the surfaces adds materially to the general comfort. The *ice-cap* frequently relieves headache without the addition of medicine. The extremities of these patients should be kept warm; for this purpose hot-water bags or bottles well covered to prevent burning, or an electrotherm, may be used. The mouth, lips and nares should be carefully cleansed and albolene frequently applied to prevent dryness and cracking. The healing of herpes may be hastened by the application of spirits of camphor, followed by albolene or boric ointment.

Chill.—If the physician is called during the *chill* (this does not often happen), he should surround the patient with hot bottles or water bags and may give a goblet full of hot water with thirty drops each of aromatic spirits of ammonia and compound spirits of lavender; if this is not at hand, a cup of hot tea or coffee will be found efficient. During the initial chill the hot mustard foot bath adds greatly to the patient's comfort, and cuts the chill short. This should be given with the patient in bed, and need not disturb him.

Pain and Cough.—Early in the disease the *pleuritic pain and cough* are annoying, with more or less malaise, headache, and myalgia. Under these conditions .03 (½ gr.) *codeia phosphate,* subcutaneously administered, with .6 (10 gr.) aspirin may be given. These remedies may be repeated in two hours. If the pains are not relieved, .01 (1/6 gr.) *morphia* sulphate may be given hypodermically; the codeia will, however, prove sufficient in many cases. Added relief is given by *strapping* the affected side, carrying the adhesive plaster well beyond the median line in front and behind, overlapping these to give added strength. As much relief to pain may usually be obtained by using a tight binder about the chest. If properly applied, it will remain in place. With the binder there is less danger of irritating the skin than with the use of adhesive plaster. Many female patients complain bitterly of abdominal pain due to straining of the abdominal muscles from coughing. Here again a firm binder gives great relief. Prompt relief often follows the use of the ice-bag or the compound mustard liniment, 8 gm. (ʒij); the latter is poured on absorbent cotton, held against the painful side by means of the bandage during fifteen to twenty minutes; this does not blister, it reddens the skin, and acts as a powerful counterirritant. The application of large flaxseed poultices to the chest frequently gives complete relief from the pain. In all places where local applications are made careful attention should be paid to the condition of the skin. During the following twelve to twenty-four hours *pain* is best controlled by either morphia in small doses, or from ten to fifteen drops of the tincture of opium and ipecac, given every three, four, or five hours, according to the urgency of the symptoms. The addition of the ipecac is helpful. In children small doses of tincture of opium and ipecac (.06 to .12, one to two drops), according to the age of the patient, will prove of great value, while the effect on the general condition of the patient, and associated symptoms in the adult and in the child, is usually favorable. The relief of pain accomplishes several important objects: it promotes expectoration, relieves congestion, assists the pulmonary circulation, eases respiration, relieves depression, and rests the patient. With involvement of the lower lobes, pain is not infrequently referred to the abdomen, and the physician should always be on his guard against mistaking such a pneumonia with abdominal pain for an acute abdominal condition, as appendicitis. It is not impossible that both conditions may be present at the same time, as in one case seen by the writer, though, of course, this must be extremely rare.

Gastro-intestinal Tract.—In all cases of pneumonia it is wise at the very beginning to empty the gastro-intestinal tract thoroughly, and throughout the course of the disease to bear in mind the effect of an *overfull* or *dilated stomach.* Inactive intestines add to existing obstruction, also to respiratory embarrassment and cardiac asthenia. However only mild cathartics should be used, as milk of magnesia, cascara or phenolphthalein. A daily morning soapsuds enema is usually sufficient to keep the bowels clear. When strong cathartics are used the patient usually has several movements, which are exhausting, followed by much gaseous distention and constipation. More patients suffer from distention in pneumonia from the improper use of cathartics than from the toxemia of the disease.

The fluid intake should be carefully measured. About 3,000 c.c. of fluid should be ingested daily. If plain water is especially distasteful, Vichy, orangeade, lemonade, or weak tea or coffee may be substituted.

In rare instances pneumonia is accompanied by persistent vomiting for the first few days of the disease. If sufficient fluid cannot be taken by mouth, 4 to 6 ounces of water may be given by rectum every four hours. If fluid cannot be retained and absorbed in this way hypodermoclyses of normal salt solution should be resorted to.

The urinary output should be carefully noted for each twenty-four hours. An abundant secretion of urine is an excellent prognostic sign. Small amounts of bicarbonate of soda may be used to counteract the mild degree of acidosis that sometimes occurs in pneumonia. If soda is to be used over a week's time, determinations of the alkaline reserve of the blood should be made. Even cases that excrete a weakly acid or neutral urine, as determined by litmus, may develop an alkalosis and general edema. This is especially so where chronic nephritis and hypertension is present.

Abdominal Distention.—This symptom is usually, but not always, an index of the patient's intoxication. When it becomes marked it may very seriously interfere with the circulation and respiratory movements. Its development should be vigorously combated, and this can best be done by very careful watching and proper treatment carried out while the condition is still slight in degree. Palpation of the abdomen is fully as important as percussion of the chest in the routine physical examination. With the slightest sign of distention the diet should be restricted and milk and fruit juices discontinued. In the mild case peristalsis should be stimulated by the use of glycerin suppositories. Where this is ineffectual turpentine stupes should be applied. They may be applied as rapidly as needed for twenty minutes, then omitted for twenty minutes, and again repeated. The insertion of a rectal tube often aids in the expulsion of gas. It is advisable to allow the rectal tube to remain for some time.

At the Presbyterian Hospital, New York, the following enema is frequently given with excellent results. It consists of a mixture of:

Fel bovis	ʒi
Turpentine	ʒii
Asafetida	ʒiii
Soapsuds	1-2 parts

This is retained as long as possible, and followed in one hour by soapsuds enema. Care must be taken, however, not to unduly exhaust the patient by too frequent and persistent use of large enemas.

Occasionally all these methods bring little relief, and in such cases temporary improvement may follow the use of pituitrin given intramuscularly in 1 c.c. doses.

Delirium.—The delirium of the average case, *non-alcoholic,* is easily managed by occasional doses of codeia or morphia. It does not require a large dose of morphia to quiet the patient; often small doses suffice and produce narcosis out of proportion to the size of the dose given; the sleep is likely to be profound. In the delirium and unrest of cases in the terminal stage, the timely use of morphia is often life-saving. In occasional cases, where morphia is not tolerated, veronal, trional, luminal, or medinal may be tried. Cerebral symptoms are an expression of underlying infection, often pneumococcic meningitis; with the appearance of these symptoms we consider among causative factors the changed body temperature, the heart condition, respiratory embarrassment, and we are not to overlook the possibility of alcohol as a factor in cases where its habitual use was unsuspected. In such cases it is often wise to give 15 to 30 c.c. of whisky every two to four hours, where this is not distasteful to the patient. With the first appearance of symptoms of delirium tremens 0.6 gm. of veronal should be given in the early afternoon, repeating after four hours if necessary. If this does not suffice to quiet the patient, the use of paraldehyd in 10 to 20 c.c. doses by mouth or 30 c.c. by rectum has been found safe and efficacious. In very severe cases it may be necessary to use hyoscin, but this drug should be employed with the greatest care, and its use limited to the occasional most extreme case.

DIET

The problem of the *feeding* of pneumonics, because of the limited course of the disease, is not so complicated as it is in the infections of longer duration. It is important to protect the patient without overtaxing the organs of digestion and circulation. The already enfeebled and overtaxed heart should not be called upon to perform unnecessary effort in the process of digestion.

There is a lowered nutritive activity during the development and progress of the disease; there is also a lowering of the functional ability of the organs of digestion to perform the usual amount of work; and to these factors we must add the waning power in the "oxygenating capacity of the system, due to a blocking out of a part of the air space by the pulmonary inflammation" (Potter).

Wolf and Lambert in their study of protein metabolism in pneumonia reached the following conclusions: "Cases of milder type show a smaller loss in nitrogen and sulphur than do those of a more severe grade. The daily loss in nitrogen on a diet adequate to protect a resting individual from nitrogen loss may be from 20 to 25 gm.

"During the period of hyperpyrexia excessive amounts of creatinin are eliminated. This is followed during convalescence by a subnormal excretion of creatinin; this is taken to indicate the endeavor on the part of the organism to repair the losses sustained during the height of the toxemia." Large amounts of creatinin are excreted in the severer pneumonias. Wolf and Lambert found that this loss is seen particularly during the time of the greatest nitrogen loss. During convalescence creatinin disappears from the urine. "During hyperpyrexia, especially in cases severely toxic in type, unusually high amounts of undetermined nitrogen are excreted. In some cases over 5 gm. of nitrogen derived from uninvestigated substances are found in the urine." These experimenters found that sulphur excretion runs parallel with that of nitrogen, and cases which progress unfavorably seem to show an excessive destruction of protein containing much sulphur.

The available diet should be almost entirely liquid in character; it should be light, should not excite cough in swallowing, nor should it ever be given in sufficient quantity to cause marked distention of the stomach. An abundant and free supply of *water* is the first requisite in every case. Small quantities of food given at relatively short intervals are preferable. The demands of the patient average between 2,400 and 3,000 calories per diem. The aim should include the raising of "the intake and utilization of proteid material as nearly up to or a little beyond the normal standpoint as possible" (Potter). The total of food given should include from 65 to 95 gm. of proteid per diem.

Milk, eggs, broths, purées, liquid cereals, and fruit acids, with the addition of alcohol where specific indications justify its use, will in the majority of cases meet all indications for diet.

In administering *milk* it is absolutely necessary to know whether the stomach is able to digest it without holding it in large curds to irritate and add to the danger of the disease. I have seen patients whose respirations and pulse were promptly increased after taking raw milk, who were able to digest the milk when acidulated after the method of Rudisch, which includes diluted hydrochloric acid 1 part, 250 parts water, and 500 parts milk. In practice ½ teaspoonful of dilute hydrochloric acid in 1 pint of water is slowly poured into 1 quart of raw milk and brought to a boil with constant stirring. This method makes the milk palatable to many, and, for these, more readily digested than normally. Milk may be predigested, diluted with Vichy, seltzer, or limewater, added in accordance with the taste and requirements of the case. Rubner has shown that 1 liter (1 quart) of milk contains 700 calories. The average milk sold in our cities probably gives 640 calories to the quart (Meara), or 20 calories per ounce. We cannot, therefore, depend on milk alone to nourish the pneumonic, as the amount of the liquid required to give the needed calories (2,400 to 3,000) would be out of proportion to the patient's digestive ability; therefore, cream, barley, sugar, sugar of milk, rice water, or oatmeal may be added, and these are usually well borne. Water-ice, ice cream, cup custards, orange juice with or without whipped albumen, lemonade, grapefruit, grapes, koumiss, matzoon, zoolak, and often buttermilk are enjoyed and promptly digested; vegetable soups are permissible.

Coffee.—The average adult is stimulated by a cup of coffee or tea given thrice daily. In the late stages of the disease strong coffee per os, and at times per rectum, does yeoman's service.

Alcohol.—The use of alcohol in pneumonia is not usually essential, though small amounts offer an added number of calories in easily assimilable form.

If it is made clear that in the individual case the prescribed diet without alcohol is insufficient to meet the caloric requirement or if there are other indications, then alcoholic preparations, as heat-producing foods, should be added. Alcohol is not necessary in all cases, but the experienced know that there are cases in which it is absolutely indicated. Pneumonics show great tolerance for alcohol, and it is in all probability used as a food as well as a stimulant. The individual case offers its own indications, and these must be reported by the cautious nurse and interpreted by the discreet physician. Diluted alcohol, whisky, brandy, tokay wine and champagne offer a selection from which choice may be made.

If proteid animal food increases intestinal fermentation, or if by it a culture medium in which bacteria proliferate is supplied, to the detriment of the patient, as is shown by discomfort, a change will be needed, and vegetable broths, already suggested, may be substituted; these added to alcoholic preparations may occasionally bridge the patient over the critical period. "Owing to the greater ease of digestion, and the higher nutritive value of the animal class, this class is more frequently called into service than is the vegetable class alone. Owing to lower nutritive and higher caloric value and antibacterial influences, the vegetable class can often be utilized to greater advantage" (Potter). Potter further emphasizes the fact that "judgment and skill must be exercised in changing from one class to the other, lest nutritive activity be allowed to fall to too low an ebb, and the heart muscle be starved to death." *Alcoholic subjects demand alcohol during the active period of the disease.*

Without it we often face collapse. Effervescent drinks should be cautiously used; fresh cold water or ice pills are preferable. To quench thirst orange juice, raspberry vinegar with water, diluted phosphoric acid with syrup of raspberry, the latter so much used in Germany, may serve this purpose. During convalescence ripe fruits are grateful, as are vegetable purées, calf's foot jelly, omelet, and junket. Let the return to a liberal diet be postponed until the fever has subsided and the patient is on the road to recovery.

HYDROTHERAPY

The *fever* of pneumonia is one of Nature's provisions to destroy the pneumococcus; at the same time it is likely to be an expression of the virulence of the toxemia. As a rule, the temperature in pneumonia does not call for active interference. The pneumococcus cannot long thrive in a temperature of 104° F. Cases with high temperature from the beginning, in which there is a free and frank development of the disease, often run a shorter course and are more likely to terminate in crisis than are those in which the temperature is low, gradually rises, without the typical picture of the "honest pneumonia." High temperature with marked remission during even a limited period daily requires no antipyretic treatment, as a rule. Fever persistently above 104° to 106° F. demands attention both in children and adults. A convenient order is for an alcohol sponge bath every four hours if the temperature is above 102.5° F. Sponges should be discontinued, however, if they prove disagreeable to the patient. Higher temperatures are not often encountered; when present, they require hydrotherapeutic measures as the safest method of treatment, if there are no contra-indications. With high temperatures there are often evidences of heart weakness, which influence us materially in the selection of the method of overcoming hyperpyrexia. Cold is not well borne in the presence of heart weakness. Often the hot sponge bath under covers, one extremity after the other, with cold to the head, reduces temperature without causing fatigue or shock. This method is particularly valuable in the pneumonia of early life and with patients who are restless and who show increasing heart weakness.

Ice and cold locally applied "exert an undeniable temperature effect on the deeper structures" (Schweinburg). Schweinburg claims a lowering of temperature when ice is placed on the surface. Measurements were taken in the mouth, vagina, the bowel, and pleural cavity to prove the contention. Cold to the thorax and to the head in pneumonia does positively affect the heat-regulating centers, and should be used in well-selected cases. There is often a prompt response in the mitigation of symptoms referable to the central nervous system. The patient besides having less pain is quieter and less irritable. The Leiter coil has frequently proved an agreeable substitute for the ice-bag. In the very young and very old cold locally should not be used; in these cases heat is preferable. Whenever ice-bags are used, one of these should be applied over the consolidated area.

Rubbing the surface with ice with proper stimulation has occasionally relieved hyperpyrexia in desperate cases. Ice-bags should be removed whenever temperature is within the limit of safety, unless they are needed to relieve pain.

Immersion into the cold bath should remain untried if other methods are efficacious, or if, in the presence of high temperature, the pulse remains good and there are no evidences of more than the ordinary wear from the fever. When the patient shows evidences of pulmonary edema, increasing heart weakness, cyanosis or an approach to it, or labored respiration, in spite of high temperature, the indications referable to the heart must be first met, and these do not often include or allow the full bath in the average case. There are many factors to be considered before using the full cold bath in pneumonia which require quick judgment. The profession is agreed that tubbing in pneumonia is not followed by the average good results obtained with the same treatment in typhoid fever. The Germans use the full bath oftener in the treatment of pneumonia than do the Americans. The cold bath with effusion gained a firm hold in Germany after the appearance of von Jürgensen's article many years ago. Liebermeister's treatment includes cold baths (70° to 80° F.) in the beginning, 85° F. toward the end of the febrile period. These are of ten minutes' duration and are given, when the temperature of the patient is 104° F. or above, between 7 P. M. and 7 A. M. Liebermeister gave no baths during the daytime, but cold sponging, and by this method reduced his hospital mortality to 16.5 per cent.

Experiences in this country have not led the profession to follow the routine use of tub baths in the treatment of pneumonia. Baths are not only useless but injurious if the disease is progressing favorably. Strümpell's statement that "almost every bath has some disagreeable feature" is justified.

Preëxisting heart lesion, myocardial degeneration, or coronary disease offer positive contra-indications to the use of the bath in pneumonia.

The blanket pack (Kellogg) followed by the cold mitten friction occasionally answers every purpose. In the asthenic type of the disease the wet sheet often produces sleep in the midst of active delirium.

In my hospital service and private practice I have usually decided in favor of cold sponging with the use of cold compresses or ice-bags to the thorax and have rarely been disappointed; patients have not revolted as they invariably do when immersed. Cold to the skin stimulates sensory nerve endings, to the general circulation and to the vasomotor nerves of the pulmonary vessels it is a powerful stimulant, also to the respiratory center and to the cerebrum; in fact, the total effect on the nervous system has usually been salutary. For the general practitioner in the average cases the cold sponge and cold compress or ice-bags properly applied offer more than any other hydrotherapeutic measure, and with less danger and inconvenience to the patient.

There are many cases in which heat does more than cold, and we are not surprised to find, considering our own experiences, that Ortner became a convert to the use of the hot bath in the treatment of pneumonia. He recommends that it be used early for the purpose of encouraging perspiration, believing that toxins are thus eliminated. The effect is increased by the drinking of large quantities of fluid. In the malignant types of toxemia Ortner recommends the hot bath with intravenous saline injection. In this he was anticipated by Henry years ago. During the cold season, when pneumonia prevails, if the open-air treatment or an approach to it is carried out, hydrotherapy will not often be required; during the heated term when we see less of the disease occasional cases may demand it.

MEDICINAL TREATMENT

While this article considers in detail the treatment of the many indications which are present during the course of pneumonia, and suggests the use of a variety of remedies from which choice may be made to meet these, there will be, in the practice of every rational therapeutist, many cases in which he will be able to pilot his patient to recovery with a minimum of medicine. In most cases sufficient digitalis to digitalize the heart muscle, caffein sodium benzoate to stimulate the respiratory center, and codein to control cough and pain will be all the medication required.

Quinin and Its Salts.—The enormous doses of quinin given by the Germans thirty years ago are no longer used. At the present time, prompted by the experiences of Petzold, Henry, and Solomon Solis Cohen, the *quinin and urea hydrochlorid* is rapidly gaining a place for itself in the therapy of pneumonia. Cohen has recently called the attention of the profession to the use of this double salt of quinin. He was prompted by Gailbraith's use of quinin in large doses (1904). Cohen uses the most active salt, quinin and urea hydrochlorid, as advised by Petzold for malaria, hypodermically, in his hospital service. As a rule, from 6 to 10 gm. (90 to 150 gr.) are given in divided doses in from forty-eight to sixty hours. The initial dose is from 1 to 1.6 gm. (15 to 25 gr.), followed in three or four hours by a second injection and perhaps by a third and more, according to the effect and urgency of the symptoms. Following the use of the remedy there is no cinchonism, in spite of the fact that smaller doses, 0.3 to 0.6 gm. (5 to 10 gr.), are given by the mouth for several days after the use of the remedy hypodermically.

The temperature and pulse fall gradually and proportionately; the respiration more rapidly; there is a tendency to restoration of the normal pulse-respiration ratio. Blood-pressure is either unchanged or increased. Cohen says: "The complete clinical picture so far as regards the rational symptoms (objective and subjective) is thus favorably changed." Patients are more comfortable after the injections, pulse is full and strong, respiration easy, cough is materially relieved, delirium favorably influenced. Lysis between the fifth and eleventh day was found in the majority of cases; there was no crisis. Physical signs are uninfluenced. The invasion of new areas again demands recourse to the injections. Empyema was not prevented. The most striking improvement in respiratory symptoms, cardiac vigor, holding and improvement of blood-pressure, led to the logical inference that the results are chemical and antitoxic. Cohen's mortality does not exceed 10 per cent. There are no bad results attributable to the drug. The use of the double quinin salt does not exclude the administration of other remedies to meet indications, and should be followed by the tincture of ferric chlorid. Cohen says: "I would not like to be called to treat pneumonia without this important resource at hand." Petzold considers the use of quinin hypodermically as a specific and considers it the most valuable of the recent contributions to the treatment of pneumonia. He uses quinin hydrochlorate. Henry subscribes enthusiastically to the quinin injection treatment for pneumonia, using hydrochlorosulphate of quinin because of its greater solubility.

The double salt of quinin and urea hydrochlorid is soluble in water; a 50 per cent solution in sterilized water is most convenient. Of this solution from 1 to 2 gm. (15 to 30 drops) may be administered hypodermically, followed by a second injection in from three to four hours, or, as Cohen suggests, perhaps by a third and even fourth injection at some time within the first twenty-four hours, according to results. On the second day this plan of treatment is repeated, and on the third, if necessary. From 6 to 10 gm. (90 to 150 gr.) are given in from forty-eight to sixty hours; after this time smaller doses, .3 to .6 gm. (5 to 10 gr.) may be given daily by the mouth for several days. It is wise to follow Cohen's directions, which are as follows: "The syringe is filled with a 50 per cent solution of the quinin and urea salt in sterilized water, and the needle is inserted deeply through the skin, previously painted with iodin, into a muscle. The syringe is emptied thoroughly, so that the solution does not drop upon the skin when the needle is withdrawn. The point of puncture is sealed with iodoform-collodion." No bad results follow these injections made in the manner recommended.

Caffein.—Caffein should be given in the early days of the disease only in small amounts. It should be administered in the form of coffee or tea, three or four cups a day. It is a convenient way to increase the patient's fluid intake and it promotes a sense of well-being. The diuretic action of caffein lessens to some extent the toxemia. A large amount of caffein in the early stages of the disease is not indicated, as it frequently increases nervous irritability and insomnia.

When respirations begin to increase in the later days of the disease, the dosage should be increased, for caffein is the best respiratory stimulant one has. Here caffein sodium benzoate hypodermically in doses of 0.25 gm. (3¾ gr.) every four to six hours is most efficacious.

All hypodermic medication, especially with women, should be given in the thighs. For not infrequently in severe cases of pneumonia with bacteremia, pneumococcus abscesses develop at the site of injection of even non-irritating drugs. These abscesses on healing often leave disfiguring scars.

Camphor.—Seibert of New York (1909) insisted that 20 per cent *camphorated sterile oil* should be injected in large doses as soon after the initial chill as possible. Recently he has recommended the use of 30 per cent camphor oil. The remedy is repeated every twelve hours, giving 10 c.c. (ʒiiss) of the prepared oil hypodermically to every 100 pounds of body weight. In cases of bilateral pneumonia and severe toxemia, these injections are repeated every six to eight hours. Seibert believes that the camphor destroys the vitality of the pneumococcus in the blood current, and that small doses are without effect. His results are encouraging. The Germans have for years used camphor as a routine remedy in the treatment of pneumonia, more particularly for the weakness of the heart.

Creosote Carbonate.—Favorable results sometimes follow the use of *creosote carbonate* or *creosotal* (Van Zandt and W. H. Thomson). Van Zandt claims to have reduced the mortality to 5 per cent by the use of creosote carbonate. Thomson uses creosotal and reports but 1 death in 18 cases, these including 3 double infections and 2 alcoholics, 1 having delirium tremens. He administered 1 gm. (15 gr.) every two hours while the patient was awake without bad effect on the kidneys. The cases are likely to terminate by lysis. The dose of creosote carbonate is .45 gm. (7½ gr.) every three hours for several days, continuing after the temperature is normal for a limited period; otherwise there will be irregular rises. Sajous' treatment consists in the free use of saline solution with creosote carbonate from the very beginning, to replace the sodium chlorid which is consumed with abnormal rapidity in pneumonia; normal osmotic properties are preserved and undue viscosity prevented. The creosote carbonate "enhances the bacteriolytic and antitoxic power of the blood and enables the blood to reach the nidus of infection with increased rapidity."

He gives 0.6 to 1 gm. (10 to 15 gr.) in capsule every two or three hours.

Guaiacol.—*Guaiacol,* either for its effect on the lung tension or temperature, is mentioned to be condemned. When used as an antipyretic, its effect is produced at a loss of the patient's resistance. The same may be said of *pilocarpin.*

OXYGEN

The literature bearing on the value of oxygen in the treatment of pneumonia is contradictory. Recently, however, the brilliant work of Stadie at the Hospital of the Rockefeller Institute has placed our knowledge of the action of oxygen in disease conditions on a firm scientific basis.

According to Stadie, "the use of oxygen as a therapeutic agent is rational only when, by reason of a disturbed metabolism or an insufficient oxygen supply, either local or general, there exists a condition of suboxidation. There are many causes of suboxidation, but the one which interests us here is commonly called anoxemia. Anoxemia may be defined as that condition in which the hemoglobin of the blood is less saturated with oxygen than normally.

In considering the passage of oxygen from the arterial blood to the tissues two factors must be recognized: normal blood has available for tissue respiration about 20 volumes per cent of oxygen (capacity factor) at a tension (intensity factor) ranging from 100 to 0 mm. Hg. The average normal amount of oxygen taken by the tissues from the arterial blood is 6 volumes per cent, or 30 per cent of the total capacity. The dissociation curve of average human blood (Barcroft, 1914) shows that when the arterial blood is completely saturated, the 6 volumes per cent will be delivered to the tissues at a tension greater than 35 mm. Hg. In other words, the amount of oxygen ordinarily used is available at this relatively high tension. The remaining 16 volumes must be given to the tissues at relatively low tension (less than 35 mm. Hg.).

If, however, the blood in the arteries is only partially, for example, 70 per cent, saturated, there are still available for the tissues 14 volumes per cent of oxygen. This is more than enough for ordinary purposes. But this oxygen is at a tension less than 35 mm. Hg. A person with this degree of anoxemia is in extreme distress. Although the oxygen of his blood is abundant in amount, it is available at low pressures only; so that unless it is assumed that the tension at which the oxygen is available for tissue metabolism is of as much importance as the total amount, it is difficult to understand how such a condition of anoxemia can be harmful.

In pneumonia there frequently occurs a condition of anoxemia. While there is no direct evidence to show that this acute anoxemia, often of profound degree, is harmful, nevertheless it is usually assumed that the presence of anoxemia is dangerous. In a series of thirty-three pneumonia cases (Stadie, 1919) there was only one case which recovered in which the arterial unsaturation of the blood was greater than 20 per cent. A high degree of anoxemia in pneumonia, then, is accompanied by a high mortality, and yet it must be distinctly remembered that they are not necessarily cause and effect, since the degree of anoxemia varies directly with the severity of the infection and the extent of the consolidation. It is possible then that the anoxemia is simply a concomitant feature of intense and extensive infections and plays no rôle in the ultimate fatality. Not until the relation of function to oxygen tension is further elaborated can it be definitely said that an anoxemia *per se* is a factor in the fatal outcome.

Since anoxemia is a frequent and often a pronounced symptom of pneumonia, a study of the effects of oxygen upon this type of anoxemia and upon the course of the pneumonia was begun and is here reported. The anoxemia is due to an insufficient aëration of the blood in its passage through the lungs. As to the mechanism of this deficient aëration, it is usually assumed that the consolidation of part of the lung, the presence of many small patches of infiltration extending from the main or initial focus, the plugging of many small bronchi, and the coating of the alveoli with exudate and moisture diminish the respiratory surface or hinder the diffusion inward of oxygen. This explanation does not stand alone, and recently Meakins (1920) stated that: "The anoxemia occurring in acute lobar pneumonia is the result of the rapid and shallow breathing typical of this condition" which purely mechanically lessens ventilation of the alveolar spaces. In both cases the administration of oxygen would tend to relieve the anoxemia by greatly increasing the percentage of oxygen in the alveolar air and hence its diffusion pressure.

In critically ill cases of pneumonia, then, it is conceivable that anoxemia might make serious inroads upon the resistance of the patient and hasten the end. Certainly experience has shown that cases with an arterial unsaturation greater than 20 per cent usually proceed to a rapid and fatal termination. In these cases the relief of anoxemia might prolong life until the forces of immunity could assert themselves.

Stadie reports in detail his experience with eight cases of pneumonia which were treated in an oxygen chamber which he devised. The chamber itself measured 10 by 8 by 8 feet and had a total capacity of 640 cubic feet. Devices for the automatic regulation of the amount of oxygen in the chamber and the removal of carbon dioxid and other waste products were installed. It was possible to administer oxygen in this chamber for long periods of time under exactly known conditions. Prolonged inhalation of oxygen varying from 40 to 60 per cent appeared to be without harm. Oxygen administered in suitable amounts caused a disappearance of anoxemia and cyanosis except in a few instances where there was marked edema and extensive infiltration of the lungs.

Five cases in which the prognosis was grave recovered. Three cases died, one of tuberculosis, one with a pneumococcus Group 3 infection, and a third with a pneumonia superimposed on a chronic pulmonary condition.

To Stadie's cases may be added two patients from the writer's private practice. A woman of forty-eight years, with a Group 1 pneumococcus infection, on the thirty-fifth day of her disease was admitted to the Hospital of the Rockefeller Institute for special study. The patient's condition had steadily become worse over a period of ten days. There was no evidence of resolution. There was a moderate amount of sterile fluid in both pleural cavities, general edema, anuria, and rapid shallow respirations, 64 per minute. There was marked cyanosis and moderate delirium.

This patient was treated in the oxygen chamber with 40 per cent oxygen for five days. There was immediate improvement. The cyanosis cleared, respirations fell to 32 per minute, and the edema disappeared with the return of normal urinary excretion.

The second case was a young woman of twenty-eight years with a very diffuse bronchopneumonia associated with an atypical Group 2 pneumococcus. For eleven days her condition became steadily worse, the signs of infiltration of the lungs increased and the cyanosis deepened and the respirations rose to over 60 per minute. With 40 per cent oxygen the cyanosis and delirium disappeared and the patient made a good recovery.

Whenever respirations rise above 40 per minute or become labored, oxygen should be used. The especially devised chamber used by Stadie is, of course, not usually available. The administration of oxygen by using a funnel suspended above the patient's nose, as well as the spatula advocated by Meltzer and various masks, is disappointing. Very satisfactory results, however, can be obtained by introducing a soft rubber catheter properly lubricated into the nares until the tip reaches the nasopharynx. The catheter is retained in the nose by a strip of adhesive plaster applied to the cheek. A catheter used in this way does not annoy the patient and may be retained for a period of several days. Oxygen is allowed to bubble through the wash bottle about sixty to one hundred bubbles per minute. In this way oxygen may be administered continuously as long as it is indicated.

Oxygen must be freed of chlorin before it becomes safe; otherwise it irritates the membranes of the air passages. It must pass through a wash bottle before it is inhaled. Ozone may be added to prevent deterioration. Saline infusion, with timely venesection or local abstraction of blood by leeches or wet cupping, is of value in connection with inhalation of oxygen, as well as such other depletion as will relieve the heart by thoroughly emptying the splanchnics, preferably concentrated solutions of salines, administered early in the morning when the stomach is empty.

In asphyxia, in which toxemia is associated with a pronounced mechanical element, Raymond and Maissonet have used hypodermic injections of oxygen with remarkable results.

"The technic is very simple. The skin of the outer surface of the thighs is first disinfected with tincture of iodin, and a sterilized needle is then pushed into the subcutaneous cellular tissue. Care must be taken to be assured that the needle is not in a vein, to avoid gaseous embolism. To the needle is then attached the tube from an oxygen cylinder. This tube should have an interruption of a glass tube containing a little sterile absorbent wool, which acts as a filter. Then the gas is allowed to bubble gently under the skin. The injection is kept up for about twenty minutes. The quantity of gas injected is not measured." This subject is treated in Chapter II of this volume, and the reader is referred to this for full details.

TREATMENT OF THE HEART IN PNEUMONIA

The excellent work of Porter and Newburgh has done much to discredit the assumption that death in pneumonia is due to cardiovascular paralysis and toxic degeneration of the heart muscle. They found that disturbances of the respiratory mechanism were of much greater importance.

In the treatment of young adults with apparently normal hearts, cardiac stimulation is rarely necessary. During the summer of 1918 at Camp Jackson, South Carolina, a group of 195 pneumonias among the soldiers was treated without the use of any heart stimulant. No cardiac irregularities were noted except occasional premature beats. The mortality in this series was 7.7 per cent.

Digitalis.—On the other hand, a certain number of patients suffering from pneumonia, usually those in the sixth and seventh decade of life, develop cardiac irregularities. Cohn has shown that digitalis acts in the pneumonia patient exactly as it does under other conditions. It is in these cases that the use of digitalis may be life-saving. Inasmuch as it is impossible to predict which case will develop auricular fibrillation or flutter and which will not, one feels much safer in digitalizing the heart muscle early in the disease. There is no evidence to show that digitalis does any harm when used in proper dosage. Even in the few instances where heart block has resulted from overdosage no unpleasant symptoms have developed.

In using digitalis it is very important that a standardized preparation of the drug be employed. At the Hospital of the Rockefeller Institute, digitan (formerly digipuratum) has been used over a period of years with almost constant results. One c.c. of a good tincture is equal to 0.1 gm. of digitan. It is now possible to procure digitan for hypodermic use where speed of action is essential.

The drug is given in doses of 0.1 gm. at intervals of two hours. After 1 gm. of digitan is given by mouth one can usually obtain electrocardiographic evidence that the heart muscle is digitalized after from two to fifteen hours, depending on the rapidity of administration.

Following the advice of Cohn, the drug is administered by mouth as follows:

Day of disease.......	1	2	3	4	5	6	7	8	9
	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
If patient is seen early	0.5	0.5	..	..	0.5	0.5	..	..	..
If patient is seen late	..	..	..	1.0	..	0.5	0.5	..	..

The indiscriminate use of such remedies as lower the vitality of these patients, while they reduce temperature, is injurious and interdicted. All antipyretics, except cold or heat, which suddenly depress temperature do so at the expense of vital force, and are apt to rob the patient of needed resistance, and may cause sudden collapse. Nothing should be given which, at any time in the course of the disease, acts as a cardiac depressant. Let the treatment from the beginning be constructive, not destructive.

In spite of the authoritative statement of Von Jaksch that coal-tar preparations "are nervines and indispensable," we strongly oppose their use in pneumonia.

Nitroglycerin.—The indiscriminate use of *nitroglycerin* as a heart stimulant is fallacious; it widens vessels and the heart is given an added tax. It has been demonstrated also that the vagus is paralyzed; thus inhibition is removed from the heart by large doses of the drug, and it is assumed still further by Brunton that the blood loses its power of absorbing and conveying oxygen, conditions which should be prevented.

Nitroglycerin may have its uses in overcoming peripheral obstruction where the arteries are tense, sclerotic, or narrowed, against which the heart is laboring. This condition is occasionally present in pneumonia of the aged, and may be associated with interstitial nephritis. Experience with these cases has been very unfortunate; with slightly lowered pressure due to the drug, and a slow pulse during a short period, the heart finally fails and the patient dies.

Veratrum Viride.—The author has never seen a case of uncomplicated pneumonia materially relieved or controlled by *Veratrum viride.* In strong plethoric subjects with high blood-pressure and a great deal of pulmonary congestion Sajous believes that Veratrum viride and the bromids in full doses relieve the patient. He believes the drug depresses the vasomotor centers, forces more blood into the splanchnic area, while the peripheral organs and lungs are depleted.

In chronic nephritics suffering from pneumonia, with advanced arteriosclerosis, aortic insufficiency, likely to be of the afebrile type, the author has occasionally relieved discomfort by the use of the drug.

The routine use of Veratrum viride should be discouraged; the reduction of temperature and heart force by its use is fraught with danger and has not the slightest influence on the pneumonic process; this becomes more clearly pronounced during its use; neither does it reduce the febrile period. Sidlo, who made thorough observations at the Duchek Clinic, concludes that "Minor variations in the febrile symptoms are proved to depend not on the action of Veratrum viride, but on the character and amount of the inflammatory process in the lung." The disease increased, diminished, and terminated to all appearances just as if nothing had been given. Vomiting, collapse, and other unpleasant effects often follow the use of the drug.

Caffein Sodium Benzoate.—Caffein sodium benzoate, 0.03 to 0.06 gm. (½ to 1 gr.), is the one drug given by the writer in all pneumonias from the beginning because of its bracing and stimulating effect without doing harm. It is best given hypodermically. This salt of caffein is soluble. When face to face with marked cardiac or respiratory depression, acute or threatening collapse, the dose must be materially increased, giving as high as 0.12 gm. to 0.36 gm. (1 to 4 gr.) with the diffusible stimulants as often as four to six times in twenty-four hours.

I have not infrequently tided patients over the critical period by the rectal injection of three or four ounces of strong *coffee,* followed by the Murphy drip of normal saline and coffee, continued during several hours at a time, if the rectum continued tolerant. *The usual dose of caffein as given by most physicians is too small to produce results.* Caffein stimulates the vasomotor centers in the medulla, it raises blood-pressure by causing contraction of the vessels; this action is not accompanied by a slow pulse, but by some acceleration; the action on the muscular fibers of the heart, however, causes more powerful contractions besides increasing urinary secretions. The fact that the blood is in a measure depleted of its water by the action of caffein on the kidneys and that the supply is replenished from the tissues makes it necessary to balance the loss by the drinking of abundant water, by the rectal drip, or, in threatening cases, by saline hypodermoclysis. Henry is a pioneer in the use of saline hypodermoclysis; his results have often been paralleled by the writer in serious cases (normal saline 3, ad 500; 50 gr. ad 1 pint).

Strychnin.—At the present time the profession is skeptical concerning the efficacy of *strychnin* in the treatment of pneumonia. The feeling against its use is growing. Dock does not consider strychnia indicated in the heart complications of pneumonia. "Strychnin is sometimes given, never necessary as a routine remedy, never indicated at a particular day in all cases, and I cannot yet admit its usefulness in circulatory weakness" (Dock).

Adrenalin Chlorid.—*Adrenalin chlorid* is an exceedingly powerful drug in the treatment of the cardiac weakness of pneumonia. Pye-Smith and Beddard make the statement that it is "in fact, by far the most powerful circulatory stimulant which we possess," to which Sajous subscribes; he believes that the adrenals, thyroid and pancreatic secretions jointly supply the blood all its "immunizing constituents." The adrenal is in the ascendancy ("the amboceptor in the immunizing trio"). *It is best injected directly into the muscle or given with saline hypodermoclysis.* When blood-pressure is low it often proves of value to bridge the patient over the critical period. *Edema of the lungs,* where the patient is drowning himself in his own serum, is best treated by other remedies, for it is likely to increase the edema in some of these cases. The development of glycosuria during its administration is not a direct contra-indication to its use, for this is likely to happen. *The drug should be given only during limited periods,* because of the danger of necrosis of the liver. From ten to thirty drops of the 1 to 1,000 solution of adrenalin may be given every one, two, or three hours, according to the urgency of the symptoms.[2]

Strophanthin.—Fraenkel first reported his experiences with the intravenous use of the drug in 1-mg. doses. He holds that it is an active cardiac stimulant, most powerful in desperate cases of pneumonia, where prompt results are desired. The writer's experiences prove it to be *dangerous after digitalis has been used during several days, or in large doses.* The action of strophanthin is much like digitalis, the pulse is slowed and becomes stronger. If used in too large doses, heart block may follow, the heart becomes irregular, blood-pressure falls, and death follows. It should be injected directly into the vein, being *careful not to introduce it into the surrounding tissues, for it is an irritant to connective tissue.* The median basilic vein should be selected. Both Stone and

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[2] Adrenalin chlorid is the most valuable remedy we have in the vasomotor paralysis of pneumonia. The toxins of pneumonia act not only upon the vasomotor centers but upon the splanchnic nerve as well, paralyzing it and causing overfilling of the blood-vessels supplied by it. As a result so much blood may be collected in the splanchnic area that general circulation becomes impossible. As soon as the evidences of splanchnic paralysis present themselves adrenalin should be given. It should be administered by hypodermoclysis in normal saline solution. As soon as the symptoms begin to disappear caffein sodium benzoate is substituted for the adrenalin, which should be given by mouth as soon as possible.—Editor (Billings).

Liebermeister believe that its use enables a certain number of severe cases to be carried along until toxemia is eliminated, and to reach the road to recovery. Stone uses 1 mg. repeated in twenty-four hours. When the drug acts favorably blood-pressure is raised, urine is markedly increased, the heart becomes stronger and resumes its work. Stone considers the free diuresis as being exceedingly favorable, for the "toxic products seem to him to be more rapidly eliminated than would otherwise be the case."

The intravenous use of digitalis preparations is attended with considerable danger. Crystalline g-strophanthin is the best form of the drug to use. The first dose should not be more than 0.3 to 0.5 mg. It may be repeated at hourly intervals to a total amount of 1 mg. Strophanthin should never be used on patients who have previously had digitalis.

Babcock has seen sudden death from 0.5 mg. Vickery thought in one case he saved the patient's life; in some cases he found it a wonderful stimulant, and believes that "it is capable of giving the patient a short time longer of life, so that, if the crisis is almost due, he may get over the bar into the harbor."

Disastrous results will probably be reduced if standardized preparations are used. One mg. of Boehringer's strophanthin is so graduated that it is supposed to kill twenty frogs of given size. Strophanthin may be considered a stable preparation; Boehringer's strophanthin imported in ampullæ is reliable and standardized.

It is important to notice that Hatcher states "that the amorphous strophanthin varies somewhat in activity, but so far we have found no variation in the activity of the crystalline." Boehringer's strophanthin is an amorphous preparation. The degree of variability is not given by Hatcher, but experience has shown that the strength of this preparation may vary within unsafe limits. Caution is therefore urged in its use, especially when it is given repeatedly. It should under no circumstances whatever be given if digitalis has been employed any time within at least a week.

Camphor.—Camphor should be administered hypodermically in increasing doses as cardiac asthenia increases; it should be given as soon as digitalis is indicated, and may be given in 20 per cent sterile camphor oil with a small addition of ether. This offers the best mixture for injection. It should be given in appreciable doses. When danger threatens, from .18 to .3 gm. (3 to 5 gr.) may be injected every one, two, or three hours. All recent writers argue in favor of this time-honored remedy [3] (Leonard Weber, Seibert, Craig, Hare, Strümpell, Meara, etc.).

In hospital service and in private practice in desperate cases I have averaged as high as 40 gr. of camphor per diem during three to four days. Musk is often given with camphor and caffein.

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[3] One may be legitimately skeptical of the value of a drug which may be given ad libitum without producing toxic effects.—Editor.

Babcock recommends the following mixture:

Musk, 1 gm.	gr. xv
Alcohol, 1 gm.	gr. xv
Sodium benzoate, 0.5	gr. viiss
Water, 15	ʒiv

Filter; mix.

A large amount of this filters very slowly because of the impurities in the Tonquin musk—(0.06 gm. ad 1 c.c.) (musk 1 gr. ad 15 gr.).

In young children camphor, 0.03 gm. (½ gr.), may be administered by the mouth with *benzoic acid* and sugar, where repeated hypodermic injections are objectionable.

Spartein Sulphate.—*Spartein sulphate* has been commended for its effect on the right heart, but the results have been disappointing, as a rule.

Diffusible Stimulants.—The secret of the rational treatment of cardiac asthenia must be found in such methods as restore or sustain heart strength and arterial tone during the period of stress. The *diffusible stimulants* sustain heart force during short periods only; unfortunately their effect is evanescent.

The writer's plan of treatment includes the administration of these at very short intervals during the continuance of cardiac asthenia. The stimulating effect must be continuous during the critical period. To get results the remedy must be repeated before the preceding dose has lost its effect; in other words, the fading effect of the preceding dose must be met by the strength of the following dose. In no other way can we accomplish the desired result in desperate cases.

I have administered every fifteen minutes, during periods of stress, fifteen drops each of the compound spirits of ether, aromatic spirits of ammonia, compound spirits of lavender, and tincture of valerian. This is kept up day and night until the pulse shows improved tone and the heart action is better, when the intervals are lengthened.

The valerian is added because of its quieting and tonic effect when administered in these small doses with the diffusible stimulants. Some critics without having used this treatment have feared stomach revolt; this rarely follows; when it does the compound spirits of ether has been temporarily omitted and whisky has been substituted, or the dose of the ammonia and lavender was doubled. The frequent administration of the compound has not seemed to annoy the patients; they are not disturbed, but swallow automatically.

Blood-Pressure.—Whenever possible, a daily record of the blood-pressure should be kept. It may often lead to the early recognition of circulatory embarrassment.

It is however, the consensus of opinion now that Gibson's rule, "*When the arterial pressure expressed in millimeters of mercury does not fall below the pulse rate expressed in beats per minute, the fact may be taken as an excellent augury; while the converse is equally true,*" is not of as great prognostic significance as was first hoped it would be.

The studies of Newburgh and Minot led them to conclude: (1) that "blood-pressure measurements in pneumonia cannot be used as a basis for treatment"; (2) that the "prognostic inferences based on the relation of the level of the systolic pressure curve to the pulse curve (Gibson's rule) are wrong more often than they are right in this series"; (3) that "low systolic pressures are not invariably of evil omen." Rapidly falling systolic pressure, especially if accompanied by a marked increase in the heart rate, may, however, indicate grave circulatory disturbance.

Venesection

Sydenham (1624-1689) considered venesection his leading remedy for the treatment of pneumonia. Many authorities still approve of its use early, in robust, full-blooded patients, with a bounding pulse and high arterial tension. There are unquestionably cases of dilated and weakened right heart in which a timely venesection does yeoman service; these patients are, as a rule, plethoric, are likely to be alcoholics, flabby, and often abnormally fat, with surface venules chronically overfilled. If we could make clear the fact that the tension in the right heart is relieved so that its systole becomes more effective in dispelling its blood into the pulmonary artery by means of venesection, we would rarely hesitate. This we cannot always promise; but we do occasionally accomplish the desired result.

It may not always be wise to abstract "one pint or a pint and a half," as S. West recommends, but watching the patient and removing the quantity considered safe in well-selected cases, under conditions mentioned, is a rational maneuver. In all cases where the heart is laboring with an excess of blood the question of venesection must be considered and conclusions reached after a thorough consideration of associated symptoms. The leading indications are right-sided heart failure, with labored breathing, cyanosis, contracted pupils, distended surface veins, and profound toxemia. McPhedran says that the robust will bear almost any treatment, and will usually weather the storm. This has not always been my experience, particularly if toxemia is profound. The Gambrinus type of pneumonic is likely to show evidences of cardiac failure and pulmonary edema after the third day of the disease, though his pulse was full, slow, and tense early. He is a good subject for venesection, and cautious treatment of what surely follows, with or without blood abstraction, that is, cardiac asthenia. McPhedran is correct in his conclusion that patients with "ordinary vigor, or those even far from being robust, when they show the danger signals of a dilated or dilating heart," show some relief from venesection. It is unsafe to recommend bleeding in all these cases, however. It will be practical in but a few of these, but its indications ought to be considered oftener. The abstraction of from 200 to 400 c. c. of blood will suffice in the average case.

Rochester quotes an English confrère in favor of venesection, who considers it scientific treatment because it helps "to make the blood clean and keeps it circulating." In the midst of a threatening pulmonary edema venesection should be considered, and local abstraction of blood by means of leeches is positively indicated. The use of hot fomentations when congestion is at its height, to promote bleeding after the use of six to eight *leeches,* is frequently practiced by the English and Germans, and often with relief of the overburdened heart and the pain. Kidd believes that for the relief of pain there is nothing to compare with leeching. There can be no object in entering into the discussion of the *modus operandi* of bleeding, whether the improvement is due to the direct relief of the pulmonary circulation or the toxemia. Reduction of blood-pressure in the pulmonary circuit, according to Reid, supplies the key to the treatment of pneumonia; he makes the statement that cases amenable to treatment "will recover if some means is adopted of reducing blood tension in the pulmonary circuit at that time in the course of the disease when the pressure is approaching its height, that is, about the third or fourth day, and preceding the crisis." He believes that there is anatomical proof that bleeding in the intercostal space relieves tension in the pulmonary circuit; abstraction from the intercostal spaces diminishes the flow from the azygos veins and thus diminishes tension in the pulmonary circuit. Reid's plan has been to apply two or at most three leeches over the consolidated area, allowing them to drop off in their own time and then keeping up warm fomentations for thirty-five minutes, following this with morphia.

Treatment of Complications and Sequelæ

During the height of the disease if the patient is annoyed by frequent coughing, especially if this is accompanied by pleuritic pain, it is wise to use small doses of codein (32 mg. or ½ gr. every four hours if necessary). In convalescence where the sputum is abundant, more rarely scanty, inhalations of compound tincture of benzoin or creosote two or three times a day often afford relief.

Crisis.—The treatment of the patient during crisis demands, besides close watching, absolute rest, quiet, repeated reassurance, heat to the extremities, stimulation in accordance with the indications offered by the circulation and reduced temperature, the occasional administration of ethereal stimulants and adrenalin and regular use of digitalis, caffein, and camphor, according to the symptoms present in the individual case. The dangers of crisis have been exaggerated; attention to detail without much medicine, and proper diet, with a bracing cup of coffee at short intervals, added to the strong personality of the nurse and physician, will be sufficient to carry the majority of patients to convalescence.

Delayed Resolution.—*As a rule so-called "delayed resolution" is due to some discoverable complication.* However, occasionally this condition is present and demands treatment. The general health and nutrition of these patients require direction. Climatic treatment should be considered. Deep breathing should be practiced and encouraged under the personal supervision of the physician. Externally the compound soap poultice and iodin may be used. Calcium, ammonium, or sodium iodid often prove useful. Edsall and Pemberton report successes from the application of X-rays. The cases treated by these investigators were promptly influenced by the remedy, the consolidated areas clearing with, at the same time, a marked increase in the metabolic output through the urine; thus the features of normally resolving pneumonia were reproduced. Fibrolysin (Merck) has been recommended in these cases. *No case should be considered to be one of "delayed resolution" or "unresolved pneumonia" until a thorough process of differentiation has made the diagnosis positive.* Tuberculosis or empyema will be found in the majority of cases.

Acute Otitis Media.—By far the most common complication of pneumonia is otitis media. In every case the eardrums should be inspected upon the first examination. All cerumen should be removed in order that the drums may be clearly seen. If this precaution is taken at the outset, confusion will not arise later as to the cause of a red drum, infection or manipulation.

As a symptom of middle-ear infection, deafness is much more common than pain. Rupture of the eardrum and the appearance of pus at the external auditory meatus may take place with absolutely no pain. Consequently it is necessary to make frequent inspections of the eardrum. If there is reason to suspect purulent infection of the middle ear, the drum should be freely incised.

Bilious Pneumonia.—The so-called bilious pneumonia may be treated much like the typical disease—giving attention to the greater and earlier cardiac asthenia and to the organs of secretion and excretion. Free diuresis, abundant water, salines, and catharsis with salicylates deserve consideration. The use of rectal salines and hypodermoclysis in these cases have occasionally helped to bridge the patient over the critical period.

Pneumonia of the Alcoholic.—In this article we have frequently referred to indications offered by the alcoholic sick with pneumonia. In the treatment of this condition, which is, as a rule, fatal to these subjects, we would refer the reader to suggestions already made. It may be positively stated that alcoholics demand alcohol; without it they collapse. A sufficient quantity is demanded to assist in the nourishment of the patient, and to keep up the pulse. Nervous excitability must be allayed; the patient must be protected against himself by proper nursing and medication. Hyoscin, morphia, chloral, paraldehyd, and ethereal stimulants are included in the remedies, from which selection may be made. The choice of the remedy for the individual case demands considerable thought and modification, in accordance with changing conditions. The alcoholic should receive the needed supply of liquid, his thirst must be allayed. The heart gains strength while the alcoholic sleeps. His wild delirium wears him out. In the majority of the severe cases there is "wet brain," that is, alcoholic meningitis which often antedates the pneumonia.

Afebrile Pneumonia.—There are cases of afebrile pneumonia which pass to crisis or lysis with positive physical signs. These are not infrequently of grippal origin. They are most frequently found among the aged, with arteriosclerosis or renal complications. There is great danger in these cases of sudden cardiac asthenia and overpowering toxemia. The diagnosis may be missed; once made, the cases demand thorough watching. The indications for treatment are offered by the heart and pulse, while all processes of elimination must be guarded.

Pneumonia of Diabetics.—The pneumonia of diabetics offers an exceedingly grave prognosis. In these cases the general tonic plan of treatment suggested in this article should be followed, and alkaline waters liberally administered. Occasionally this treatment is rewarded with success. The majority of these cases are atypical and present complications demanding special attention.

Pulmonary Edema.—There is an unfortunate class of cases with early heart weakness and pulmonary edema, in which the lung is promptly flooded. These patients really drown themselves in their own transudate and often die during the first thirty-six hours of the disease, in spite of any known treatment. When face to face with such threatening conditions, the free use of cups and venesection are positively indicated, more particularly if the patient is plethoric. To these may be added mustard foot baths, while the hypodermic use of atropia and morphia with other cardiac stimulants hypodermically administered may occasionally lead to improvement. These methods are simply time-saving in their effects; they may make it possible to bridge the patient over a critical period; for, the toxemia being short-lived, we may on rare occasions find ourselves transported to a clearer and more favorable atmosphere.

Meningitis.—Meningitis as a complication of pneumonia is always fatal except for that associated with the meningococcus. Though cases have been reported, I have never seen a meningitis due to the pneumococcus, staphylococcus, streptococcus or influenza bacillus recover.

Every case in which meningeal involvement is suspected should be lumbar punctured because of the rare chance of meningococcus infection for which the antimeningococcus serum is so efficacious. I have seen several cases of bronchopneumonia following measles or influenza which subsequently developed a meningococcus meningitis, some of which recovered with appropriate serum therapy.

In many cases the signs of meningitis are ushered in with severe headache and fibrillary twitching of the muscles about the mouth and eye; more often there is a curious calm apathy that precedes the storm. Most patients upon examination of the blood will give evidence of a bacteremia.

Complicating meningitis due to the Group 1 pneumococcus has *not* been benefited by the use of Group 1 antipneumococcus serum, whether used intravenously, intraspinously, or intracerebrally.

Acute Dilatation of the Stomach.—Acute dilatation of the stomach is an occasional serious complication of pneumonia; it is a source of great danger. When it arises suddenly during the height of the disease it may promptly lead to death. Sudden dilatation with chronic valvular lesions and pneumonia is usually fatal. Fussell has recently reported his experiences with this dangerous complication. In all of his cases the autopsy showed constriction of the duodenum at the root of the mesentery. There is in all probability involvement of the innervation leading to dilatation, this in itself causing by traction a constriction of the duodenum. These cases, which are easily recognized because of the associated physical signs, including peristaltic unrest, splashing, and collapse, demand immediate washing out of the stomach, which should be repeated according to the urgency of the symptoms. The tube may be used, though the patient is found in collapse. The patient may be turned on his side to encourage the emptying of the stomach; this maneuver without lavage is of but little value. Strychnia and eserin salicylate have been recommended, but are of doubtful value. The tube alone gives results. Meltzer suggests that the dyspnea with frequent swallowing of air without saliva may be a factor in the production of the dilatation.

Cases in which accumulation of gas is troublesome, without excessive dilatation of the stomach, are often relieved by the administration of a few drops of chloric ether on sugar with 1 gm. (15 drops) of compound tincture of cardamom. The Germans use compound spirits of ether dropped on sugar at short intervals for the relief of this symptom.

Hiccough.—A frequent complication of pneumonia, usually at the height of the disease, sometimes following the febrile period, is *hiccough.* There are cases in which this symptom is exceedingly rebellious to treatment. At times ten drops each of *Hoffman's anodyne* and *compound tincture of cardamom* on sugar, slowly swallowed, suffice to relieve. Hypodermic injections of morphia often cause a restful sleep during which the spasm ceases, and on awakening hiccough has disappeared. In many cases, however, there is prompt recurrence with great prostration, agitation, and excessive nervousness. Under these desperate conditions, when patient and physician were discouraged, musk, .06 gm. (1 gr.) in capsule every two or three hours, and an occasional morphin injection, have helped. With sustained improvement the hypodermics may be discontinued, but the musk should be continued for several days. Finally strontium bromid, 1 to 1.5 gm. (15 gr. to 23 gr.), may be given, well diluted, to produce sleep, after discontinuing the morphin injections.

Bradycardia.—Bradycardia often follows pneumonia whether treated by digitalis or without. At times this is accompanied with sinus irregularity, partial heart block, and occasionally premature beats. With bradycardia the pulse may be intermittent; this need not worry the attendant if there are no associated symptoms, and the general condition improves from day to day. The ungeared state of the heart may persist during several weeks, yielding to rest, and the usual tonic treatment given convalescents.

Tachycardia.—In some cases tachycardia becomes annoying during the period of convalescence or after pneumonia. Endocarditis may have been present in these cases; it should be suspected, as should other complications, including tuberculosis, phlebitis, hidden abscess, empyema, etc. The therapeutist will not be long deceived, for thorough consideration of associated conditions and physical examination will reveal the cause of the rapid heart. Without other complications recovery from these cardiac anomalies of a purely functional character follows in the course of time.

Endocarditis.—Acute endocarditis, which complicates nearly 10 per cent of lobar pneumonias, yields in the majority of cases to the treatment which controls the general infection. All cases should receive absolute rest and cold locally. In painful and severe cases counterirritation over the precordium is justified, if cold fails to relieve. This complication materially affects prognosis and retards convalescence.

Pulmonary Embolism.—Embolic complications in pneumonia while rare are usually fatal. This complication, in my experience, has occurred almost always in cases that had a completely consolidated lobe which did not resolve in the usual period of convalescence. The patient regains his strength more rapidly than the consolidation of the lung disappears. It is dangerous to allow a patient with pure bronchial breathing over one lobe to be up and about in spite of his feeling of general well-being.

Pericarditis.—When pericarditis is added, or when present without endocardial invasion, indications for treatment remain much the same.

Purulent and large serous effusions into the pericardium demand surgical interference without delay.

Bronchorrhea.—Bronchorrhea following pneumonia with irritating cough is an occasional complication during the period of convalescence and following. It is usually relieved by terebene, .6 gm. (10 drops), given in capsule three times daily with .6 gm. (10 drops) of fluid extract of cheken. Compound tincture of benzoin is also a valuable remedy for the same purpose.

Pleurisy with Effusion.—Pleurisy complicating pneumonia is present in most cases, and is relieved by the remedies suggested for the relief of pain under General Treatment. It is rare that the accumulation of fluid resulting from pleurisy in uncomplicated lobar pneumonia demands special treatment.

Empyema.—Empyema is, next to acute otitis media, the most frequent complication of pneumonia. It is seen most frequently with pneumococcus infections associated with Groups 1, 2, and 4 and with the hemolytic streptococcus.

It is usually not difficult to obtain fluid or pus if present in the chest by exploratory puncture. If fluid is not obtained in the usual position below the angle of the scapula, one should not hesitate to explore in the midaxillary line or anterior to this point, if physical signs and symptoms suggest pus.

Recently the question as to the best method of treating empyema has received great consideration, owing to the frequent occurrence of this complication among the soldiers in our army. Many surgeons have strongly advised against early thoracotomy because of the danger of collapse of the lung before adhesions have formed to wall off the abscess area. They have been greatly impressed with the results of frequent aspirations. In rare cases recovery has taken place without operations. It must be remembered, however, that this opinion is based largely on empyema associated with the hemolytic streptococcus, an infection that is common after measles and influenza epidemics but rare at other times.

With hemolytic streptococcus infections, this amber cloudy fluid containing streptococci may occur very early in the disease. Not infrequently fluid may develop in both pleural cavities and the lungs themselves may be the seat of a diffuse bronchopneumonia. Under these circumstances it may be wise to resort to repeated aspirations, though personally favorable results have been seen only in rare instances.

On the other hand, with empyema associated with the pneumococcus, as soon as purulent or amber cloudy fluid containing viable pneumococci can be recovered from the chest (usually not before the eighth to the fourteenth day), nothing can be gained by delaying free evacuation of pus by thoracotomy. With pneumococcus cases, collapse of the lung has never followed early operation in my experience. Adhesions have always been formed by the time the fluid has been discovered. Early operation shortens convalescence and subsequent normal expansion of the affected lung is hastened.

Abscess of the Lung.—Abscess of the lung may be suspected by the development of a harassing cough and profuse expectoration of sputum on change of position during convalescence from pneumonia. It is a rare complication. In my experience, Staphylococcus aureus has been found most frequently, with Friedlander's pneumobacillus, B. influenzæ, and streptococcus more rarely. In old abscesses there is always a mixed infection.

X-ray examinations of the chest in the upright position are often of great value in aiding the diagnosis. In early abscesses the sputum is often not fetid.

Exploratory puncture of the chest may also be very useful in detecting an abscess. If after penetrating the pleura and lung, exerting gentle suction on the plunger of the syringe as the needle is advanced, the barrel of the syringe fills with air suddenly, it is very suggestive of an abscess.

Nephritis and Pneumonia.—Chronic nephritis, either tubal or interstitial, complicated with pneumonia, presents conditions of extreme gravity, the treatment of which has been considered in connection with that of cardiac toxemia, blood-pressure study, and other associated features. Each case will demand special attention, but the general considerations presented in this article give sufficient hints to guide the therapeutist. Occasionally acute nephritis with general edema develops as a complication of pneumonia. This condition has followed in three instances where unusual delay in finding hidden pockets of pus in the pleural cavity occurred.

Convalescence.—A thorough appreciation of the effect of malign infection will be sufficient to direct the treatment of the period of convalescence along rational lines. The depressing effect on the heart muscle of the pneumonic demands a sufficient period of rest. Too many are permanently damaged because the cardiovascular system is denied the repose which is an absolute necessity after all grave infections, particularly pneumonia, typhoid, and diphtheria. Too often the attendant allows himself to be swayed by sentiment and yields to the importunities of the patient, anxious to return to his work, little appreciating the possibility of inviting permanent damage. It is unwise to set a time limit during which the patient must remain quiet and under observation; let the study of the case lead to a safe decision. Pulse, blood-pressure, the general condition of the patient, including the blood state, will aid in deciding on the time when it will be safe to venture beyond the supervision of the physician. Rest, massage, a well-selected diet, deep breathing, attention to ventilation, stimulation of the appetite where necessary by bitter tonics, the addition of an extra supply of carbohydrates, cod-liver oil where indicated, iron in easily digestible form, arsenic, the hypophosphites, malt, and lactate of lime include what is needed in the majority of cases. In some cases climatic treatment is indicated. The selection of the proper environment for the convalescent who needs a change demands the thorough consideration of many factors, and becomes an exceedingly important and responsible matter.

SPECIFIC TREATMENT AND CHEMOTHERAPY

Rufus I. Cole and A. R. Dochez

Revised by Henry T. Chickering

General Considerations

Diplococcus pneumoniæ (Weichselbaum) or the pneumococcus (Fraenkel), as it is commonly called, is a highly parasitic coccus which is widely distributed throughout nearly all habitable parts of the world. In the tropics and the regions where extreme cold prevails during a large portion of the year, the organism is much less frequently found than in the temperate zones where seasonal variations in temperature and climatic conditions are more extreme. Pneumococcus infections may, however, show a high degree of incidence in tropical and subtropical climates, affecting most severely the natives of these localities. Where such a condition has prevailed, it has followed the association of natives, among whom in their normal habitat pneumococcus infection was nearly unknown, with whites coming from regions where pneumonia was common and who probably acted as carriers of the infection. The high susceptibility of natives in such an epidemic indicates the probable absence of previous exposure to pneumococcus infection.

Although Eberth, Klebs and Koch described cocci resembling pneumococcus found in association with lobar pneumonia, the cultural methods at their disposal were insufficient for a positive identification of the organism. The discovery of the pneumococcus may be attributed to Sternberg and to Pasteur, who published almost simultaneously accounts of the lance-shaped diplococcus in the normal mouth, which was able to induce a fatal septicemia in rabbits. They, however, did not associate the organism of the mouth with the various pathological lesions which we now know to be caused by pneumococcus, and it was only after the thorough studies of Fraenkel and of Weichselbaum that the constant association of the pneumococcus with lobar pneumonia was satisfactorily determined.

The pneumococcus is occasionally met with as an infectious agent in lower animals, but it is in man that the organism finds its most favorable habitat. It is known to occur, at least at times, as a harmless inhabitant of the buccal cavity in from 50 to 70 per cent of normal individuals. As a pathological agent it is found in a variety of disease conditions among human beings. General invasion of the blood by the pneumococcus without evident local lesion has been reported. It would seem probable, however, that such a condition must be extremely rare and that in most of these cases some hidden focus has been overlooked. At least in one apparent case of this type, after diligent search a small alveolar abscess was found which served as the portal of entry. Focal lesions are by far the most common manifestations of pneumococcus infection in man. Of these, lobar pneumonia, with its complications and sequelæ, is the most important. Pneumococcus may, however, produce the lobular type of pneumonia, and is a common concomitant infection in ordinary colds and disease of the accessory sinuses of the nose. It may occur as an independent agent in disease of the middle ear, ulcer of the cornea, in purulent meningitis, in acute arthritis, and in peritonitis. Many of the focal localizations of the organism outside of the lungs, however, represent metastatic infections derived from a primary site in the lung.

The chief importance of the pneumococcus lies in its ability to produce a croupous inflammation of the lungs, which is the severest and most fatal of the acute infections which are common to temperate climates. Acute lobar pneumonia, because of its striking and characteristic clinical picture, has been recognized since the earliest times. The recognition of the disease as a definite clinical and pathological entity is the result of the eminent studies of Morgagni, Baillie, Laennec, Rokitansky and Addison.

Lobar pneumonia is an endemic and generally sporadic disease that is common throughout the United States and Canada. It is frequent all over temperate Europe, in the inhabited portions of the south temperate zone, such as Australia, parts of South America, and in South Africa. Although it is much less frequent in the tropics, it is often seen even here among the inhabitants of the plateau regions. The census of 1920 showed that in the United States somewhat over 10 per cent of all deaths were due to some variety of pneumonia. Some statistics seem to indicate that the incidence of pneumonia is increasing. That this apparent increase may be due to better methods of diagnosis is very probable. However, one may safely say that the general incidence of pneumonia has shown no tendency to diminish. This may be due in part to the general acceptance of the view of the non-contagiousness of pneumonia and the consequent lack of measures of prevention. During the same period of time such diseases as diphtheria and tuberculosis have shown a quite definite shrinkage, and one feels tempted to ascribe this to the widespread activity directed toward the limitation of these diseases. It seems to be true that the incidence and fatality of pneumonia may vary from year to year, but this is most probably associated with differences in climatic conditions. It is also possible that wavelike changes in the virulence of pneumococcus races as a whole may occur, or that the incidence of infections with the more virulent races may be more common in one year than another. In view of the fact that most individuals harbor in the mouth an organism indistinguishable from the pneumococcus, the presumption is that most pneumonic infections are auto-infections, and that the important factor in determining the incidence of the disease is a variation in individual susceptibility. Dochez and Avery and Stillman have recently shown, however, that pneumococci belonging to what are known as Groups I and II do not occur in the mouth secretions of healthy persons unless such individuals have been in intimate contact with cases of pneumonia in which infection was due to these types of pneumococci. Such an observation indicates that infection with these varieties of pneumococcus spreads either through contact with an infected individual or through association with a healthy carrier. Definite epidemics of pneumonia are not of infrequent occurrence, and generally prevail where highly susceptible individuals are exposed to infection or among persons living in close association. Such epidemics have developed as a rule in schools, hospital wards, prisons and on shipboard. Studies by Stillman, Blake and Cecil, and Park and Chickering have shown that pneumococci of Type I or Type II have been the causative agents in most of these epidemics.

Owing to the previous lack of a well-defined epidemiology and the absence of sufficient evidence showing the dependence of one case of pneumonia upon association with some preceding case, we have been forced to conclude that exposure is universal and that the incidence of the disease is determined by special conditions in the individual. Certain factors have a more or less immediate influence upon the occurrence of the disease. Statistics teach that pneumonia is commonest in early adult life, the period of greatest physical activity, though the mortality is greatest among the aged. Those who labor out of doors are more often affected than those engaged in sedentary occupations. Both of these factors indicate that fatigue, especially when accompanied by exposure to unfavorable climatic conditions, has an important influence upon resistance. Previous irritation or infection of the respiratory passages seems to act as a predisposing factor in the causation of pneumonia. At least 50 per cent of all patients give a history of a "cold" for variable periods preceding the acute onset. Whether such colds are of pneumococcus origin and the pneumonia simply represents an extension of the infection is not known at the present time. Alcohol depresses the general resistance, increases liability to exposure, and has an influence in the causation of certain cases. The predisposing effect of previous attacks is of doubtful significance as we know that various races of pneumococcus exist, and though infection with one race may confer a permanent immunity against that race, it may have no effect against infection with heterologous races.

Until study of the epidemiology becomes more widespread but little hope exists that the disease can be attacked from the standpoint of prophylaxis, and we must look forward for a time, at least, to a continued high incidence and mortality that is appalling. The physician is, therefore, reduced to consider what effective measures exist for the successful handling of the individual who is suffering from an acute attack of the disease. The problem of directly influencing the normal course of pneumonia is extremely complex and attended by what appear to be almost insurmountable difficulties. The pathological process is a rapidly developing one and the clinical onset usually fulminant and without warning. Often when the physician first sees the patient, the lungs may already be the seat of widespread infection. Of favorable import, however, is the tendency of the disease to become localized in a single lobe, and in the majority of favorable cases for this localization to be rendered permanent by rising resistance of the infected individual. Once localization is successfully accomplished, the severity of the symptoms seems to abate somewhat. The margin of safety is, nevertheless, a narrow one, and, if the virulence of the infecting organism is great or the resistance of the patient unduly low, a spread of the infectious process almost always occurs. With a spread of the process after the initial involvement, the symptoms again become increasingly severe, and it is then that the struggle for life reaches a most precarious stage, for it is during the period of such an active growth of the pneumococcus that the already weakened patient is most likely to succumb.

A progression of the disease may manifest itself in two ways. There may be an increase in the area of lung involvement, and with each successive lobe that becomes diseased the picture grows more hopeless. On the other hand, the lesion in the lung may appear to be stationary and, in spite of this, the patient rapidly loses ground and dies on from the fifth to the seventh day of the disease. Usually in such cases a serious invasion of the blood has occurred, and the pneumococcus, finding a favorable medium for its growth, develops rapidly and death is due to an overwhelming septicemia. Bacterial counts of the organisms in the blood in these cases have been found to range from one to sixty-five thousand per cubic centimeter. Often both processes occur at the same time and, with the active spread of consolidation of the lung, there is a simultaneous growth of the pneumococcus in the blood. If an efficient specific therapy is to be developed, it must meet the gravity of the situation in such severe cases and must be able to match the extraordinary rapidity with which these phenomena of the disease arise.

When confronted with an established bacterial infection, the physician has at his disposal but a very limited number of methods by means of which he can hope to influence the course of the process favorably. In the majority of instances his attempts must represent an effort to aid the lines of defense already provided by nature, or, at most, to relieve the patient of controllable embarrassments. In a few instances the medical sciences have provided us with agents which either attack directly the invading microörganism or neutralize the products, by means of which they intoxicate and destroy the host. The latter methods offer the most hopeful means of controlling an established bacterial infection, and it is to the search for such specific methods of therapy that much of the investigation of infectious diseases is at the present time directed. Until recently the artificial production of specific therapeutic agents has been carried on entirely in the bodies of foreign animals, or else efforts have been made to provoke by special methods, such as vaccination, an increased production of specific antibodies within the body of the host himself. The introduction by Ehrlich into the therapy of disease of a synthetic chemical compound with specific antibacterial action has greatly enlarged the field of specific therapeutics. All of the methods mentioned here have been tried from time to time in the treatment of lobar pneumonia.

Pneumonia belongs to a group of diseases which may be styled self-limited. Practically nothing can be done by ordinary methods to shorten the course of the disease, and recovery, when it occurs, is usually sharp and spontaneous. The rapidity with which the patient passes from a condition of extreme gravity to one of comparative safety suggests the occurrence of some quite sharp and definite reaction against the infecting parasite on the part of the host. Studies of the blood of individuals recovering from infective diseases have shown that at some stage of the process in many cases certain agents known as antibodies develop, which may exhibit a variety of specific effects upon the microörganism causing the disease. They may belong to the groups of agglutinins, bacteriolysins, opsonins, protective bodies of unknown action, or other bodies with specific reactions. The artificial production of such bodies in animals by injection of dead or living pneumococci has been comparatively easy. F. and G. Klemperer during the early years of the study of immunity demonstrated that rabbits injected with the pneumococcus or its products in culture developed in their blood serum a power to prevent infection of normal rabbits with large doses of living virulent pneumococci. The demonstration of the presence of such bodies in the blood of patients recovering from pneumonia and the relation of the appearance of these bodies to the crisis has been somewhat more difficult, and their presence and influence were doubted for many years. Recent studies have, however, shown that in most instances protective antibodies occur during the course of lobar pneumonia, and the conclusion seems justified that they play at least some rôle in the mechanism of recovery. The confirmation of these results has been of great importance, because, without such a basis for investigation, little hope could be entertained of making progress in the artificial production of such bodies and their use as therapeutic agents. There seems, then, to be sufficient scientific background to encourage the serious consideration of the usefulness of biological bodies which may be supplied artificially from the bodies of foreign animals or produced by special methods in the body of the host himself.

Consideration must also be given to the possible efficiency of some of the synthetic drugs which have recently been developed and for which a specific action is claimed. These drugs have been used independently and in some cases in conjunction with specific antisera. Products of animal cells have been utilized in the treatment of pneumonia, and certain chemical substances which acted, not against the infectious agent, but which provoked some special type of cellular reaction on the part of the host. All these various measures can probably be brought together and considered under the heading of specific therapy. Undoubtedly the most important are those which have in view the development of specific biological agents, such as serotherapy and vaccination, or the production of chemical bodies with specific antibacterial action.

SERUM THERAPY

Attempts to control bacterial infections by means of specific antisera depend upon either one of two types of action which these sera possess. Their activity may be directed either against the living organism itself and result in its death or a limitation of its ability to develop, or it may be directed against products of the bacterial cells which are diffusible and which may be able to effect injury at a distance where no living bacterial cells are present. The first type of sera are known as antibacterial or anti-infectious, the second as antitoxic. Antitoxic sera, such as we have in the case of diphtheria and tetanus, have proved the most efficacious of the antisera which have been produced so far. Attention of investigators was early directed to the search for toxins produced by the pneumococcus and to attempts to develop an immunity to such possible bodies. So far the demonstration of a soluble toxin derived from the bacterial cells of pneumococcus that is in any way comparable to diphtheria toxin has not been successful. The Klemperers tested the toxicity of broth cultures from which the bacteria had been removed. Although it was possible to kill animals with this material, such large quantities were required as to render it unlikely that the toxic action could be due to the presence of substances analogous to true toxins. These solutions also possessed some immunizing qualities which were dependent, doubtless, upon the presence of a certain quantity of bacterial protein derived from disintegrated organisms. That the pneumococcus does not, under the ordinary circumstances of bacterial growth, form highly toxic bodies, and that even large doses of the living bacterial bodies can be given without toxic action unassociated with a general bacterial infection, render it unlikely that an antitoxic serum of the type of diphtheria antitoxin can be produced. More recently substances have been prepared from bacterial bodies by special methods which seem to be more nearly related to the soluble toxins. These substances produce the type of death seen in acute anaphylactic shock, and have been tested largely on such susceptible animals as the guinea pig. Friedberger, who was the first to prepare these bodies from bacteria, has called them anaphylatoxins, and is inclined to attribute the intoxication arising in infectious diseases to substances of this nature. Dold first prepared such a substance from the pneumococcus. By submitting pneumococcus to the action of a specific antibacterial serum and subsequently digesting the sensitized bacterial bodies with guinea pig complement, a toxic body is formed which kills guinea pigs acutely in a few minutes. The mode of death resembles very much that seen in acute anaphylactic shock. Substances of like nature have been subsequently prepared by Rosenow by allowing the bodies of the pneumococcus to undergo autolysis in salt solution, and by Cole by dissolving the bacteria in bile, in which they are readily soluble. Attempts to immunize animals against these bodies so far have been failures, although antibacterial sera prepared from horses by the injection of living virulent pneumococci may have a slight neutralizing effect. General opinion holds that these substances are not toxins of the type of diphtheria toxin, which is probably a true protein, but represent some intermediate stage in the digestion of bacterial protein which is toxic. Support is lent to this view by the fact that when bacterial digestion with complement or bacterial autolysis is allowed to go on for too long a time, the toxic qualities of the mixture disappear. On the other hand, the work of Cole suggests that these bodies may be preformed in the bacterial body and represent the endotoxins of Pfeiffer. It is by no means established as yet that the toxemia of infectious diseases is dependent upon such artificially produced bodies, and the fact that in all likelihood they are disintegration products of protein renders it unlikely that anything in the nature of antitoxic immunity can be developed against them.

Attempts to prepare specific antibacterial sera whose object is the destruction of the bacterial body have been more hopeful. Such sera are highly specific in their action, and for their proper preparation and use require a refined and detailed knowledge of the bacteriology of the infection in which they are to be used. Though pneumonia of a lobar type may be produced by organisms other than the pneumococcus, and, in some instances, such organisms may act in conjunction with the pneumococcus, for practical purposes in a study of the specific therapy of pneumonia it is sufficient to consider the pneumococcus alone as the causative agent.

Shortly after the definite establishment of the causal relationship of the pneumococcus to lobar pneumonia by Fraenkel and by Weichselbaum, experimenters began to study the immunity-producing qualities of this organism. Attempts were first made to develop an active immunity in experimental animals. A. Fraenkel made the fundamental observation that rabbits which had survived a subcutaneous injection of living pneumococcus were later immune against a subsequent injection of a fully virulent culture. Other observers later confirmed this result and were able to call forth an active immunity against the pneumococcus in a variety of ways. Foa and Bordoni-Ufreduzzi were able to protect animals against fatal doses of virulent pneumococci by previously injecting them with attenuated cultures of pneumococcus. F. and G. Klemperer obtained active immunity by the use of cultures killed either by heat or by the addition of carbolic acid. Emmerich and also Mennes were able to get a high degree of active immunity by first treating their animals with killed or attenuated cultures and later submitting them to injection with increasing doses of living, highly virulent organisms. The later work of Neufeld indicates that the highest degree of active immunity can be obtained in this way. Other means and various products of the pneumococcus have been used for active immunization, but the evidence favors the use of living virulent bacteria as the most useful method.

As soon as it had been determined that animals could be actively immunized against pneumococcus, observers turned their attention to the practical use that might be made of this phenomenon in the treatment of lobar pneumonia in man. Efforts were first made to transfer the immune principles developed in an actively immunized animal to other animals, which were then exposed to experimental infection. These experiments were early successful and a number of investigators have been able to protect animals against experimental infection with pneumococcus by giving either previously or simultaneously with the infecting dose a small quantity of the blood serum of an actively immunized animal. The results of treatment in animals, however, as contrasted with prevention or protection, have not been so satisfactory. While a very small amount of serum will usually protect an animal from a large dose of bacteria given with the serum or a very short time afterward, even a large amount of serum usually will not cure the animal after infection is well advanced. Evidence is not lacking, however, that even in animals such immune serums may have curative as well as protective action. Efforts at treatment have usually been attempted in rabbits or mice, which are extremely susceptible to pneumococcus infection and in which the infection runs a very rapid course. When injections of pneumococci are made directly into the lungs of guinea pigs, the infection runs a slower course, and Neufeld and Ungermann have shown that in such cases, if injections of even small amounts of serum are made as late as three hours following the infection, recovery occurs in a large proportion of the animals. These experiments in the production of active and passive immunity in animals to pneumococcus are so striking and fundamental that it is little wonder that efforts to find methods for using the sera obtained therapeutically in man were begun more than twenty years ago by the Klemperer brothers, and are still being persisted in in a number of places where medical investigation is carried on.

Attempts to utilize the serum produced by immunization of animals as a curative agent in cases of human lobar pneumonia were first carried on by F. and G. Klemperer. They treated 18 human cases with serum derived from highly immunized rabbits. In some of these cases they observed a permanent fall in the temperature and in others only a temporary lowering. Their trials were not carried further, nor were those of Foa and Scabia nor of Jansson, who also thought that they had obtained beneficial results by the use of immune rabbit serum.

Many attempts at treatment have been made with the use of sera obtained by immunization of the horse or the ass. Washbourne reports the treatment of 6 cases with horse serum. Three of these seemed to be benefited, 1 died, and in the other no effects were noted. Pane, who has prepared an antipneumococcus serum by the immunization of the donkey, treated 32 human cases with this serum. All but 3 of those who were treated in the advanced stages of the disease recovered. According to Pane, the serum effects an improvement in the subjective condition and a lowering of the temperature. A number of other observers have used Pane's serum and report favorable results following its use. On the other hand, Banti and Pieraccini, who treated 21 cases with Pane's serum, failed to get any beneficial results. Spolverini, using the same serum in 11 cases, thought that the results were slightly favorable, but claims to have obtained the same effects by the use of normal horse serum. Eyre and Washbourne have shown that samples of Pane's serum sent to them protected animals against infection with four strains of pneumococcus which they had, but failed completely to protect against a fifth strain. Cantieri found that Pane's serum influenced somewhat the fever and general condition of the cases he treated, but had no noticeable effect on the outcome of the disease. In America Anders has collected 535 cases of pneumonia which have been treated by specific serum. Of these, 474 received antipneumococcus serum, and 61 cases antidiphtheritic serum. Of these, 85 died showing a mortality of 18.3 per cent. Of course, those treated with antidiphtheritic serum should be excluded from the statistics, inasmuch as this could not be considered a form of specific serum therapy in pneumonia. Anders holds that the results observed in the serum-treated cases of pneumonia reviewed by him were not sufficiently favorable to warrant its introduction as a general method for the treatment of the disease. The majority of American investigators who have employed antipneumococcus serum of the usual type therapeutically, coincide with this view.

Certain observers, on account of the earlier doubtful results obtained, have endeavored to interpret them and to improve the methods for the production and administration of antipneumococcus serum. Tizzoni and Panichi have attributed the unfavorable results obtained from the use of antipneumococcus serum to the fact that the organisms used for the immunization of animals were grown on an unsuitable medium. To correct this, they employed a specially prepared bouillon in which they claimed that the pneumococcus formed toxins of the same character as those formed in the animal body. They claim to have been able to kill quickly animals injected with doses of such cultures. Animals were immunized first by the injection of filtrates and later by the full culture. Care was taken in the time after injection of bleeding the animals, inasmuch as Tizzoni and Panichi found that the time of maximum concentration of antibodies in the blood varied in different animals, and that the high mark was of short duration. The authors obtained in this way sera which in doses of 0.25 per cent of the body weight of rabbits protected against a simultaneous intravenous injection of 0.2 c.c. of a virulent pneumococcus culture, whereas the control animal died in twenty-four hours. They were able also with like doses of serum and culture, the culture being given first subcutaneously, to cure rabbits after the appearance of the pneumococcus in the blood. In one instance where larger doses of serum were employed, an animal recovered when the control had died before the test animal received the first dose of serum. Such results, if reliable, indicate a serum of extraordinarily high potency. Panichi treated 7 cases of pneumonia with intravenous doses of from 15 c.c. to 30 c.c. of this serum and says that in all cases the administration of the serum was followed by beneficial results, and a fall of the temperature by lysis. In view of such striking experimental and therapeutic results, it is surprising that no further observations on the action of the serum seem to have been made.

Römer sought to increase the efficiency of the serum prepared by him in a different way. Instead of immunizing a single animal and using the serum thus obtained, several animals were chosen, including horses, cattle and sheep. After each had been immunized to a sufficient degree, they were bled, the serum obtained mixed together and used for treatment. By using antibodies derived from different sources, it was hoped to obviate the possibility that certain individuals might fail to complement the antibodies of the serum if these were derived from a single source, whereas by furnishing a multiplicity of antibodies, the chances of the treated individual's possessing suitable complementing bodies were increased. In the later methods of preparing the serum, this complicated method was abandoned, as was also the use for purposes of animal immunization of strains of pneumococcus cultivated directly from human material. Single animals were used and these were immunized by the injection of multiple strains of living highly virulent organisms, a method previously recommended by Emmerich, Mennes and others. Römer's polyvalent serum, prepared both by the earlier and later methods, has been and is still used extensively, both in the treatment of ulcus serpens and in lobar pneumonia. A number of men have reported the character of the results obtained by the use of this serum. Pässler treated 24 cases, of which 4 died and 20 recovered. In favorable cases the course of the disease was shortened. As a rule, in from six to twelve hours after the administration of the serum, a notable drop in temperature occurred. The infection seemed to assume a lighter character after the serum, the subjective feelings of the patient were improved, and the circulation was favorably influenced. In 6 cases crisis occurred after the first injection, and in 4 cases, after the second injection. The serum was administered in from 10 to 30 c.c. given subcutaneously. Crux also obtained favorable results in 12 cases, observing a fall in temperature, beneficial influence on the pulse, and shortening of the course of the disease. Crux administered the serum in doses of from 2.5 to 5 c.c. subcutaneously, repeated in twenty-four hours. The quantities of serum given by this observer were so small that it seems doubtful if the effects observed could reasonably be attributed to the action of the serum. Knauth treated 7 cases, all of which recovered. He employed larger doses of serum, from 20 to 60 c.c. Beyer observed some decrease in the mortality in 21 cases treated with Römer's serum. Other investigators did not obtain such favorable results. May observed a favorable subjective effect, but no influence in hastening the crisis or on the course, temperature or extension to other lobes. Lindenstein observed a favorable subjective effect and a drop in temperature following injection which, however, soon rose again to the previous height. Of 16 cases treated by Winkelmann with doses of from 10 to 40 c.c., 5 died, showing a mortality of about 30 per cent. Steyrer using large doses of serum could not produce a critical drop in the temperature. Jürgens observed no favorable effects following the use of the serum. The combined 44 cases treated by Pässler, Winkelmann and Lindenstein showed a joint death-rate of 25 per cent, a result which is conclusive evidence against any marked influence on the mortality-rate.

The studies of Neufeld and Händel and their associates on the preparation and action of antipneumococcus serum seem to mark a very distinct advance over the methods employed by previous observers. In immunizing the horses from which the serum was obtained they employed large doses of living virulent pneumococci. The cultures selected depended upon a careful serological study of several strains of pneumococcus obtained from human material. Previous observers had recognized the probability of the existence of different varieties of pneumococcus and in their immunization work frequently used a multiplicity of strains. The relation of one strain to another had, however, never been satisfactorily tested. The investigations of Neufeld and Händel were carried on with strains of pneumococcus isolated from cases of pneumonia. Sera of high potency were obtained from rabbits, donkeys and horses by immunization of these animals with a single strain of pneumococcus. The sera thus obtained protected to the same degree as with the original strain against most of the other highly virulent strains of pneumococcus in their possession. There were, however, certain strains which, although they could not be distinguished by ordinary methods from the strain of pneumococcus used for immunization, were not influenced in any degree by the action of the serum. Equally efficient immune sera could, however, be prepared from these strains, and it was furthermore found that these sera protected animals neither against the first type strain nor was there cross protection between these two atypical strains, as Neufeld calls them. These observations at once make it evident that the type of organism concerned in the production of any case of pneumonia is of primary importance from the standpoint of specific therapy. For the successful immunization of animals, strains must be employed which include as far as possible such types as are met with in cases of human infection. Failure to obtain good results in particular instances of the disease require an investigation of the type of organism concerned in such a case before it can be determined that the lack of success is due to failure of the serum and not to an attempt to influence a strain which is insusceptible to the action of the serum.

Neufeld and Händel also contributed important observations on methods of titration of the potency of antipneumococcus serum, and on the dosage and best methods of administration. Previous investigators had paid little attention to the potency of their sera, whereas Neufeld and Händel developed a method for testing the protective value on animals. Mice were injected with a constant quantity of immune serum and shortly afterward with varying doses of a culture of pneumococcus of standard virulence. By such a method the virulence of the organism was determined and the number of fatal doses against which a given quantity of serum would protect. In this way it is possible to maintain some standard of efficiency of the serum.

In the earlier studies of the action of antipneumococcus serum in human cases relatively small doses administered subcutaneously were employed. Neufeld and Händel have recommended the use of much larger doses intravenously. In titrating immune serum against varying doses of pneumococci by injection into mice, they have shown that a certain amount of serum in relation to body weight is required to protect. This amount protects against many times the lethal dose. On the other hand, a slightly smaller dose may not protect at all, even against only a very small multiple of the minimal lethal dose. In other words, such a serum does not obey the law of multiple proportions, and to be efficacious, even against a very mild infection, it must be present in the body in a given concentration. This concentration they have called the "Schwellenwert" or threshold concentration. Reckoning from their experiments on mice, they estimate that in man the curative dose of the variety of serum tested by them must be at least 75 c.c. It is evident, therefore, that one reason why antipneumococcus serum has not been more efficacious in the past is that it has not been administered in sufficiently large doses.

The serum of Neufeld and Händel has recently been prepared commercially and a number of observers have reported the results obtained from its use. Weitz treated 38 cases with apparently beneficial results. The initial dose of serum was from 10 to 40 c.c. This was repeated in twelve hours, and many of the cases received several injections. Of 16 cases treated on the second day, 12 showed an apparently abortive course. Among these was one individual who showed 900 colonies of pneumococci in 10 c.c. of blood taken before the first injection. Two cases were fever-free on the third day, 10 on the fourth day and 1 on the fifth day. In 3 there was no shortening of the course of the fever. One of these, an alcoholic, died. After death the blood and organs gave sterile cultures, although before the use of the serum 10 c.c. of blood gave from 2,000 to 3,000 colonies of pneumococcus. The day following the injection the same quantity of blood showed 21 colonies and the succeeding cultures were sterile. Of 9 cases treated on the third and fourth days of disease, 9 showed a normal temperature after two days of treatment. In 2 of these cases there was no noticeable effect on the temperature. Three of the patients died, but in these the infection was a mixed one, so that the result was not clear-cut. Of 7 cases treated first on the fifth and sixth day, 4 died. Weitz concludes that the serum of Neufeld and Händel exhibits a specific action in cases of lobar pneumonia, and that this action is most manifest when the patients are treated in the early stages of the disease. The report of Weitz is of especial interest in showing the effect of the serum upon general pneumococcus infection. In his experience no case had recovered which showed such large numbers of organisms in the blood as the two mentioned. Unfortunately, in this series of cases no attempt was made to determine whether the type of organism in each individual case was susceptible to the protective action of the serum employed.

A smaller number of cases treated with the Neufeld-Händel serum are reported by Geronne. In all 12 cases were treated, among them 3 children. In the earlier cases in which small doses of serum were used, 10 to 20 c.c., the results were not especially favorable. In the later cases Geronne increased the dose of serum to 40 to 80 c.c. and found that in these cases there was a marked improvement in the general condition and lowering of the temperature and, in some instances, a shortening of the course of the disease. Normal sheep serum used in a certain number of control cases showed no such favorable results. Geronne observed that the course of the local condition in the lung was not noticeably affected by the use of immune serum.

Neufeld points out that, according to the work of Rosenow, consolidation persists in the lung even after the disappearance of living pneumococci, and argues from this that the serum could not be expected to have much effect on the local condition once the disease is well established. He emphasizes, however, the importance of the general infection and thinks that in many cases of pneumonia this is the most serious element of the disease. In addition, he thinks that the serum has some influence in preventing the development of new areas of consolidation in other portions of the lung.

The authors of the present paper have been interested in pneumococcus infections, particularly lobar pneumonia, for the past twelve years. The work was taken up with the object of developing, if possible, some form of specific therapy. In order to obtain proper material for the immunization of horses, a large number of pneumococcus strains freshly obtained from cases of lobar pneumonia were studied by Dochez and Gillespie. These studies indicate certain important reasons why antipneumococcus serum may not have proved of value in the past, and explain why even the administration of very large doses early in the disease may prove of value in only a small proportion of cases. In the past antipneumococcus serum has been administered indiscriminately in all cases of pneumonia, no effort being made in the individual case to determine the nature of the bacterium causing the infection. It has long been known that characteristic lobar pneumonia may be caused by a number of other organisms besides the pneumococcus, such as streptococcus and influenza bacillus. It is well recognized that an antipneumococcus serum cannot be effective in case the disease is due to an organism other than the pneumococcus, since such serums are as rigidly specific in their immune reactions as is antidiphtheritic serum for diphtheria toxin. It must be granted, however, that a large majority of the cases of typical lobar pneumonia are due to pneumococcus, so that if such a serum were efficacious against all such cases, the results of its administration would be manifest. Neufeld, as has been previously mentioned, found that an antipneumococcus serum prepared by him by the immunization of a horse with a given race of pneumococci was effective against the race of pneumococci used for immunization, and also against certain other races obtained from cases of pneumonia; but against still other races of typical pneumococci he found that it had practically no effect.

Dochez and Gillespie have shown that pneumococci isolated from cases of pneumonia may be divided into four groups. The organisms belonging to each of the first three groups are specific, as far as their immune reactions are concerned. An immune serum produced by the injection of a horse with a race belonging to Group I has a specific action against all the members of Group I, but has no effect on the organisms of any of the other groups. In like manner, an immune serum produced by the injection of a horse with a pneumococcus belonging to Group II or to Group III is protective against all other members of their respective groups, but has no effect against the members of any other group. In Group III are included the organisms of the type of pneumococcus mucosus. In Group IV are included all races against which Serums I, II and III are not effective. Animals may readily be immunized against any member of this group, and the serum of the immunized animal is protective against the race used for immunization. In no instance, however, has this serum been found to be effective against any other variety belonging to this group, nor against any of the members of Groups 1 and II.

Avery has studied a relatively small number of strains of pneumococcus which do not react typically with Type II serum and these have been designated Type II pneumococcus, atypical. This classification of the large number of strains studied has been made by testing out the protective value of the different types of sera prepared for white mice. By making use of specific agglutination, the same classification is arrived at as by the protection experiments.

It has become evident, therefore, that while a large majority of cases of pneumonia are due to pneumococcus, so far as immune reactions are concerned, the cases of pneumococcus pneumonia are caused by organisms of at least four different types, and, from the point of view of specific therapy, this is equivalent to saying that they are due to at least four different organisms. In 866 cases of pneumonia studied, the number of cases found to be due to organisms of the four different groups is shown in the following table:

Table I—Classification of 866 Cases of Pneumonia

Type of Organism	Number of Cases	Percentage
1	300	34.6
2	206	23.8
2 (Atypical)	58	6.7
3 (Mucosus)	97	11.2
4 (Heterogeneous)	205	23.6

It is evident from these results that in studying the effects of an immune serum on patients with pneumonia, but slight conclusions can be drawn from its indiscriminate employment in all cases. First we must know the type of organism used for its production, and, second, it must be employed only in cases due to organisms of the type used in its preparation. So far it has been possible to produce a serum of high protective power against organisms of Type I. A second serum, somewhat less efficacious, against organisms of Type II, and a third serum of still lower potency against organisms of Type III have been prepared but have not been found useful from a therapeutic standpoint. It is manifestly impossible to utilize a specific serum in infections due to Type IV, inasmuch as each member of this group from a serological standpoint represents a distinct variety. The relative virulence for adult human beings of the different groups is shown in Table II.

TABLE II—MORTALITY

Cases Due to	Number of Patients	Died	Percentage
* Type I.........	175	41	23.4
Type II........	206	62	30.1
Type III.......	97	44	45.4
Type IV.......	205	32	15.6
Total..........	683	179	26.2

* Personal communication, Dr. Russell L. Cecil. One hundred and seventy-five Type I pneumonias, Bellevue Hospital, New York City, not treated with serum.

At present, therefore, the problem of serum therapy in pneumonia has resolved itself into treating the cases due to organisms of Type I with Serum I. In order to treat the individual case, however, it is necessary to have a method of determining very promptly after the patient comes under observation the type of organism concerned. It has been found possible to do this by using the following method: When a patient with pneumonia comes under observation, a culture is immediately made from the blood and also one from a portion of sputum coughed up from the lung; or, when this is not possible, a culture is made directly from the lung by the insertion of a needle. This procedure seems to be without danger. When sputum can be obtained, a culture may be most rapidly obtained by injecting a portion of the sputum into the abdominal cavity of a mouse. After sufficient growth has occurred, usually in about six hours, the mouse is killed, the abdominal cavity washed out and the cells and fibrin thrown out by slow centrifugalization; a suspension of organisms is thus obtained. However the culture is obtained, the agglutination test is at once applied. If the Type I serum agglutinates the organism, treatment may be commenced at once.

Several other rapid methods for determining the type of pneumococcus from the sputum have been described. That of Avery makes use of the rapid growth of pneumococcus in 5 per cent glucose blood broth. Krumwiede's method consists of coagulation of the sputum by heat and the extraction of the soluble antigenic substance from the coagulum. All the rapid methods should be confirmed by the mouse method, which is the most accurate.

In view of the facts described here, it is obvious that only the most irregular results could be expected from the employment of sera prepared from organisms not previously studied in regard to their group relationship, and administered in cases in which nothing was known concerning the type of infecting organisms. If these requisites are fulfilled, theoretically, at least, antipneumococcus serum might be rendered effective. Serum prepared and tested for specificity in this manner has now been used by the authors in a considerable number of cases of pneumonia. Treatment of pneumonia with serum Type I has given very good results. In 249 cases so treated the mortality has been 9.6 per cent, which represents a considerable reduction in the mortality observed in untreated instances of infection with this type of organism. These statistics include several individuals who were moribund at the time of the first treatment, and others who died from pulmonary embolism after recovery from the pneumonia or from complicating meningitis.

The method of administration of the serum is as follows: On admission .002 c.c. of serum is injected intradermally to discover if the patient is hypersensitive. As soon as the type of organism is determined, if the patient is not sensitive to horse serum, 100 c.c. of serum, diluted one-half with salt solution, is injected intravenously. The condition of the patient serves as a guide in the later treatment. Usually the serum is not given oftener than every eight to twelve hours. The patients treated received totals of from 190 to 700 c.c. of serum. The early determination of the type of organism is of great importance, since the earlier in the disease that serum treatment is inaugurated the greater are the chances of a favorable result.

In the absence of a large number of treated cases, the efficacy of serum therapy must be based on other criteria. The effect of this serum on the temperature has been as follows: After some injections a reaction occurs, the temperature usually rises and then falls, but does not necessarily remain low. In some instances the rise of temperature has been marked, in others the rise of temperature following an injection has been only a degree or so. In all the cases except the fatal ones, the serum apparently had an ultimate favorable effect in lowering the temperature and shortening the course of the disease, though, of course, it is difficult to be sure of this. In some instances one injection of serum was sufficient to bring on a crisis. All the patients seemed to feel better following the injection of the serum, and in a number of cases the apparent lessening in the degree of intoxication was very manifest. The importance of instituting serum therapy as early in the disease as possible cannot be too strongly emphasized. In a recent report by Locke of 145 cases treated with Type I antipneumococcus serum, of 89 cases treated before the sixth day, 10 died, a mortality of 11.2 per cent, whereas of 52 cases treated after the sixth day, 15 died or 28.8 per cent.

More important than the foregoing criteria, however, are the following observations, since they have depended solely on objective procedures. First to be mentioned is the effect of the serum on the organisms in the blood. In all cases the occurrence of pneumococcus in the blood has been carefully studied. Whenever a bacteremia has existed, the organisms with but few exceptions have disappeared from the blood after a single injection of serum, that is to say within an interval of from eight to twelve hours. In general, therefore, one large dose of serum seems sufficient to sterilize the blood, and the conclusion seems justifiable that if organisms are not present in the blood, the administration of serum will prevent their entrance. Of 185 Type I pneumococcus infections, blood cultures were positive in 68 or 36.7 per cent. Of 245 Type II pneumococcus infections, blood cultures were positive in 83 or 34 per cent. Yet while the mortality of the Type II infections averaged 28.4 per cent, that of the Type I infections treated with serum was 9.6 per cent.

In previous studies of the blood of patients with lobar pneumonia, it has been shown that, as a rule, the appearance of protective substances in the blood, when demonstrable, coincides rather sharply with the period of critical fall in temperature and the disappearance of symptoms. Before the crisis they are not present in the blood in any measurable degree. A similar study has been made of the protective substances in the serum in a number of cases of pneumonia treated with the authors' immune serum. In all the cases studied it has been possible to demonstrate the appearance of such substances in considerable amounts in the serum following the administration of immune serum, even when this serum has been administered early in the disease, at a period when such protective substances are otherwise never present. These substances persist, and in case they play a part in the mechanism of recovery, as has been concluded from previous studies, it is evident that their appearance indicates a favorable action of the immune serum.

The clinical and laboratory study of a series of cases of pneumonia treated by the injection of large amounts of appropriate serum seems to indicate that a method has been devised for the successful specific treatment of at least a portion of the cases of acute lobar pneumonia.

In reviewing the work done on the serum therapy of lobar pneumonia, one sees a continuous progress in the efficiency of the methods of production and administration of antipneumococcus serum. In the earlier observations but little attention was paid to the potency of the serum or to the characteristics of the organisms employed in its production. The authors of this article have been able to use potent antipneumococcus serum known to be active against the organism producing the disease in the individual with strikingly beneficial results.

On account of the frequency of "serum sickness" following the use of antipneumococcus horse serum, many attempts have been made to develop a practical method for concentrating therapeutic serum. Avery has demonstrated that all the protective substances lie in the globulin fraction. Recently Felton has succeeded in separating this globulin fraction in a highly purified and concentrated state, precipitating the globulin by diluting the whole serum with ten volumes of water, washing the precipitate with water and redissolving in a weak acid or alkali. The Felton globulin solution is said to have all the protective properties of the whole serum and its therapeutic use is said to be devoid of serum sickness complications. If the potency of the Felton globulin solution can be controlled, it will no doubt prove another important step forward in the therapy of lobar pneumonia.

The degree to which antipneumococcus serum may be employed in the future must depend largely upon the constancy with which the serological groups of pneumococci previously mentioned are found. In the discussion of these organisms, it was shown that it would be impossible to treat cases specifically with sera against three of the groups, because in one of these groups the organisms are of distinct varieties, and the other two do not yield a serum which confers passive immunity.

Every effort has been made by various methods of immunizing horses and even other suitable animals to produce an effective therapeutic serum against Type II and Type III pneumococcus without results up to the present time.

Recently Huntoon has made commercially practicable a method first suggested by Gay and Chickering for obtaining the antibodies from antipneumococcus serum almost free from protein yet combined with a minimal amount of antigen. Huntoon has produced an antibody extract from a horse serum containing antibodies for pneumococcus Types I, II, and III.

Cecil and Larsen have now used this substance in the treatment of over 400 cases observed simultaneously with over 450 control cases not specifically treated

Table III shows a very definite decrease in the mortality of the Type I pneumococcus infections and a smaller decrease in the Types II, III and IV infections.

Conner reporting a smaller group treated at the New York Hospital had a similar experience with the use of antibody extract.

As the intravenous use of the antibody extract sometimes causes alarming chills, Cecil has used it subcutaneously but with disappointing results.

TABLE III—DEATH-RATE FOR CASES THAT RECEIVED ANTIBODY COMPARED WITH DEATH-RATE IN THE CONTROL WARDS

	Treated Cases			Control Wards		
Type	Cases	Deaths	Death-Rate Per Cent	Cases	Deaths	Death-Rate Per Cent
I	157	21	13.4	175	41	23.4
II	78	22	28.2	76	31	40.7
III	57	20	35.0	60	24	40.0
IV	109	17	15.6	137	31	22.8
Total	401	80	19.9	448	127	28.3

VACCINOTHERAPY

In turning from the question of specific serum therapy of pneumonia to vaccine therapy, which represents an attempt to stimulate to a point of increased utility those forces which the body is already marshaling to combat the disease, one feels the necessity of proceeding with considerable hesitation. The advance of serum therapy has in the main gone hand in hand with scientific advances in experimental methods made in the laboratory. Aside from the early studies of McDonald, who seems to have been able to induce artificial crises in rabbits infected with pneumococcus by the administration of a vaccine made from the organism with which the animal had been infected, but little laboratory work on the curative action of pneumococcus vaccine has been undertaken. In view of the rapidity with which rabbits develop a progressively increasing septicemia, even after subcutaneous inoculation with a virulent strain of pneumococcus, it seems unlikely that such results could be repeated with any constancy. For the most part the curative action of pneumococcus vaccine has been tested on human beings, and the reports of such attempts that have been published show, for the most part, an unfortunate lack of critical judgment. While in the main the mortality statistics seem to be good, so excellent in some cases that they approach the incredible, on the other hand, most of the evidence is impressionistic in character. Such objective signs of improvement as are possible of determination do not seem to have been sought for. In a number of instances, observations, having in view the changes in immunity in the vaccinated individual, were made on the opsonic index determined by the method of Wright. This method, even with other organisms, yields information of very doubtful value, and when applied to investigations of resistance to pneumococcus is admitted, even by Wright, when the usual technic is employed, to be of no real service.

The artificial production of an effective immunity against infectious diseases has been one of the most important problems to which investigators have devoted their efforts ever since the discovery of the causal relationship of bacteria to disease. In the field of animal experimentation the attempts have been rewarded with a large measure of success. To-day in the case of a large number of disease-producing microörganisms, it is possible to protect animals against infection by previously treating them with the same virus in some modified form. The adaptation of such methods to the prevention of disease occurring under natural circumstances has also been successful in a limited number of instances. Prophylactic vaccination against such typical infections, as smallpox and typhoid fever in man and anthrax in animals, has resulted in striking diminution in the incidence of these diseases whenever vaccination has been effectively carried on. In at least one instance it has been possible to prevent, by means of artificial immunization, the development of a disease after infection has occurred. The success of the antirabic vaccination of Pasteur with a modified rabies virus, has, however, no doubt been largely dependent upon the unusually prolonged incubation period of this disease. In cases where this incubation period is short, successful employment of the method of Pasteur is less common.

The extensive work of Wright and his associates on the treatment of active disease by the use of bacterial vaccines has greatly stimulated the imagination, and, as a result, the activity of a large number of students of infectious diseases. A quarter of a century ago the procedure of injecting vaccines when the body is manifestly under the influence of the infecting agent would undoubtedly have been met with skepticism and failure. The successful immunization by Pasteur against rabies after the occurrence of infection, and in some instances even when symptoms were about to become manifest, and the apparent usefulness of Koch's tuberculin in certain cases of tuberculosis have led to a hopefulness which is still seeking justification. Wright's work on the treatment of local infections by suitable vaccines and the success which in many instances attends this method had added still further evidence in support of the procedure. The localization of an infection must, however, be regarded as the expression of a degree of immunity which is already moderately high. The great service of vaccines in this group of diseases lies in the fact that localized bacterial infections are exceedingly common, and represent in most cases an annoyance and an infirmity rather than a danger to life. In addition to these forms of infection, bacterial vaccines are now largely employed in conditions in which the specific agents of the disease can be detected in the blood, and in which the symptoms indicate that the infection is no longer strictly localized. They have been extensively employed in even such infections as typhoid fever, puerperal sepsis, general streptococcus infections, and in lobar pneumonia. Medical science unfortunately is unable to furnish an answer to the applicability of vaccines to the treatment of such infections. The appearance of such organisms in the blood in comparable infections in laboratory animals is usually rapidly followed by death. In many instances of such infections in man a like phenomenon is observed, so that it would seem from what we know of bacteriology and immunity that the employment of vaccines in such acute conditions must have a very limited field. In spite of the presumptive evidence against the usefulness of vaccines in these diseases, the method has been widely favored, especially in the treatment of acute lobar pneumonia. It seems like adding fuel to the flames, but it may be that there are unknown factors in the path leading toward immunity that the bacteriologist has not yet discovered.

In studying the reports of the treatment of lobar pneumonia by means of pneumococcus vaccine, it is extremely difficult to arrive at a just estimate of the real value of the procedure. Many observers are unhesitatingly favorable in their impressions, and yet one feels that other investigators have arrived at contrary conclusions, or at least have failed to find sufficient evidence to support a general recommendation of the use of vaccines in this disease. Unfortunately many of these studies have failed to find their way into the literature of the subject, owing probably to a natural disinclination to report unfavorable results. This fact must be borne in mind then in the consideration of such reports as are available.

In America Stoner has reviewed the results obtained from the treatment of 150 cases of pneumonia by means of pneumococcus vaccine. These include cases treated by the following observers: 14 by Wolfe, of which 11 recovered, the death-rate in the untreated controls being 40 per cent; 13 by Boellke, with as many recoveries, the average duration of the disease after inoculation being three days; 83 cases by Leary, of which 71 recovered, giving a death-rate considerably below that ordinarily observed in untreated cases of pneumonia; 1 case by Batten which recovered; 7 cases by Harris, 4 of which were benefited by the treatment showing an early crisis, and 3 which were not benefited; 1 case of delayed resolution by Allen with recovery; 24 cases by Wilcox with 23 recoveries, a truly remarkable result; 6 cases by Craig with 6 recoveries; and 6 cases by Fisher with 5 recoveries. Of the 155 cases so treated, 135 cases recovered, showing a mortality of 13 per cent. Inasmuch as the average mortality statistics in pneumonia range from 20 to 35 per cent, these figures indicate a marked reduction in the death-rate.

In Leary's 83 cases, 34 occurred in alcoholics, a class of patients in whom the death-rate is usually high. Of these 34 cases but 6 died, a mortality of 17.7 per cent. Of the other 49 cases only 2 died, a death-rate of 4.08 per cent, or a total mortality for the entire series of 83 cases, or 9.7 per cent. As far as one can determine in Leary's series of cases, autogenous vaccines were not used, and no mention is made of the source of the strains used or the care employed in their selection.

Leary admits that his results are encouraging. In the eyes of the ordinary observer they are but little short of incredible. Stoner considers the 6 cases reported by Craig of particular interest. The patients were aged, sixty-six years, sixty-seven, seventy-three, seventy-five years and five months, eighty, and eighty-three years respectively. Three of the patients were alcoholics and 2 of the cases followed an alcoholic debauch. Five had chronic nephritis and all had marked arteriosclerosis. All the cases were treated with vaccines and all recovered.

In Germany but little attention has been paid to methods of active immunization during the course of lobar pneumonia. Neufeld says that the outlook for favorably influencing an acutely progressive disease such as pneumonia, in which doubtless in all severe cases the infectious agent gains entrance to the blood, by means of subcutaneous inoculation of killed bacteria is very slight.

English writers accord more support to the method. Eyre, although he has had but little practical experience in the use of vaccines in pneumonia, favors their administration, and thinks that their beneficial action may be determined by their exhibition of a favorable influence on the opsonic index of the blood. He has found the use of vaccines especially valuable in the more chronic forms of pneumococcus infection of the lung. His opinion of the value of the opsonic index as a method for determining the degree of immunity was published some years ago and, in view of the more recent estimates of the serviceability of this method, may have been changed. Allen is rather enthusiastic in his advocacy of the application of bacterial therapy to pneumonia. He emphasizes the importance of being sure that the pneumonia in question is due to pneumococcus before proceeding with the use of a stock vaccine. He prefers to use an autogenous vaccine when possible, and recommends the stock vaccine while the former is being prepared. In criticizing adverse comment of certain other observers, he attributes their lack of a more signal sucess to the extreme rigor of their controls and a failure to use the vaccine in sufficient quantities. Morgan has treated 43 cases with an autogenous vaccine with 2 deaths, a mortality of 5 per cent; 1 of these died of nephritis after the subsidence of the pneumonia, thus reducing the mortality from the disease to 2.5 per cent. In many cases he employed repeated doses of 50,000,000 bacteria, but favors a somewhat smaller dose, 15,000,000 to 30,000,000. The temperature in some instances fell by artificial crisis and in others by lysis. From his experience Morgan thinks that the temperature may be a guide, but thinks the most noticeable feature of the treatment is the favorable change in the general condition without much change in the temperature. He does not think the opsonic index is a reliable method of estimating the progress of immunity in pneumonia, and admits the necessity of some means of determining whether or not any good effects develop which may be measured objectively. Harris reports a number of cases in the same vein and thinks that the curative inoculation of pneumonia may be successful. He adds nothing in the way of determining objectively the amount of benefit derived. Both observers agree that the inoculations seem to do no harm. Charteris, on the other hand, reports 19 cases without any observable beneficial results.

Although many of the published reports indicate no small measure of success in the treatment of pneumonia with pneumococcus vaccine, one still feels unable to accord this form of therapy a recommendation for general application. Far too few attempts have been made to gain a solid foundation for the use of pneumococcus vaccine by means of scientifically conducted laboratory experimentation. The efficacy claimed is based entirely on mortality statistics and clinical impressions, supports which are well known to be notably misleading. With the exception of efforts of doubtful utility to correlate changes in the opsonic index of treated patients with the clinical course of the disease, practically no thought has been directed toward obtaining objective evidence of improvement, such as the disappearance of a bacteremia or the appearance of readily demonstrable immune bodies in the blood. In many instances no attention has been paid to the existence of a multiplicity of races of pneumococci, and stock vaccines have been used consisting of strains about which nothing was known from an immunological standpoint. Such vaccines might easily contain only a single type of organism, or types which have no immunizing powers against the majority of types which ordinarily cause pneumonia. It is true that the best workers have sought to avoid such confusion by employing, whenever possible, vaccines made from the strain concerned in the particular case to be treated. No extended attempt has as yet been made to utilize the method of sensitization of pneumococci by specific serum antibodies in the treatment of pneumonia by pneumococcus vaccine. Levy and Aoki have shown in animals that specific immune bodies appear in the blood considerably earlier when sensitized vaccines are used than when the animals are immunized by killed cultures not so treated.

From an experimental standpoint it is difficult to find support for the efficacy of methods designed to induce active immunization in such an acute and relatively short disease as lobar pneumonia. It is well known that in the active immunization of animals, antibodies do not appear in the blood in any considerable concentration much before the eighth or tenth day, the time at which an attack of pneumonia usually terminates naturally. Besides, it is difficult to see how the addition of small amounts of antigen could measurably affect the degree or quality of immune reactions in an individual who is only too often suffering from the presence of a superabundance of substances of like antigenic properties. If bacterial vaccines should prove of value in pneumonia before their efficacy can be generally admitted, at least some of these discrepancies must be eliminated.

Rosenow and Hektoen have developed a modified vaccine for the treatment of pneumonia, prepared from partially autolyzed pneumococci. They found that on suspending a virulent pneumococcus in salt solution, the substance on which depended its insusceptibility to phagocytic action was dissolved out. The soluble portion is toxic and not only has little immunizing properties, but even interferes with the formation of antibodies in animals. The insoluble remnants have well-marked antigenic qualities, and seem to be somewhat more serviceable in protecting animals than heat-killed suspensions of whole pneumococci. For these reasons they investigated the influence of virulent pneumococci, from which the toxic portions had been removed, on the course and death-rate in lobar pneumonia. In different years the organisms were grown in somewhat different ways, and in the preparation of the antigens the cocci were allowed to autolyze in salt solution under certain conditions until most of them had become Gram-negative, a period at which they were usually sterile on cultural investigation. Some care had to be exercised to prevent the process of autolysis from going too far, because then all antigenic power might be lost. The dosage varied from 10,000,000,000 to 20,000,000,000, in some instances given once and in others repeated daily.

The cases treated were divided into three groups. The first group consisted of 30 cases treated by physicians outside of a hospital. The results in these were better than in the more unfavorable hospital cases. Of the 30 patients treated, 3 died. In the second group 35 cases occurring at the Cook County Hospital were treated. The mortality among these was 25.7 per cent. This is somewhat lower than the average mortality among cases of the same class. The third series formed much the largest group. In all, 294 cases are included in this lot, 146 having received injections of autolyzed pneumococci and 148 serving as controls. No selection was practiced, cases being taken alternately for injection and as controls. Of the 146 cases receiving injections, 34 died, a death-rate of 23.3 per cent. Of the control group, 56 died, showing a death-rate of 37.8 per cent. Comparing the two groups, one sees that in the injected series there was a lowering of the average death-rate of 14.5 per cent. In view of the very bad type of cases treated, the test was a very severe one and the results are distinctly encouraging. Many of the patients were bad alcoholics, and numbers were first injected only after the disease had become well established. In general the results were better the earlier in the course of the disease the patient was injected. The injections in favorable cases usually provoked a slight rise in temperature, followed later by a drop, the temperature thereafter remaining at a somewhat lower level. Often if the injection was repeated at this point, the temperature reached normal in from three to five days after the onset.

As the injections of vaccine are frequently followed by severe chills, Miller has emphasized the danger of these reactions and the need of careful observation of the patient by the physician following each treatment. The best results were naturally obtained in those cases treated outside the hospital because of the earlier period at which treatment could be begun. Of the cases treated in the hospital, among whom the results were not so good, the average time of the first injection was the fifth day of the disease, necessarily a disadvantage in any form of treatment of pneumonia, and particularly for the methods under consideration. The incidence of complications and sequelæ was about the same in both groups. In the injected series there was a tendency for the crisis to occur earlier than in the uninjected, especially where it was possible to start the injections early in the disease. In view of the fact that the mortality was consistently lower in the injected cases each year, that the average time of the first injection was late, and that the type of cases treated was of the worst kind, nearly one-half of the patients being bad alcoholics, Rosenow and Hektoen think that the conclusion is warranted that this method of treatment of pneumonia is of value.

From the experience of Wright, it would seem that pneumococcus vaccine might be used with advantage in the more chronic forms of pneumococcus infection of the lungs, such as delayed resolution and empyema. Indeed numbers of individuals have reported favorable results in such cases, but most of these represent isolated instances of such treatment, and no systematic study of its value in a large series of cases has as yet been carried out.

In recent years there has arisen in South Africa among the natives employed in the Rand mining district a severe type of pneumococcus pneumonia with a high death-rate and incidence. In attempting to combat this condition Wright has had an opportunity to test on a very large scale the value of prophylactic pneumococcus vaccination. After a considerable amount of experimentation, the administration of a single large dose containing 1,000,000,000 bacteria was found to be the best way in which to give the vaccine. Large numbers of natives running into the tens of thousands were available for the test. Every fourth individual failed to receive a dose of the vaccine, and these served as controls for the vaccinated. Careful records of the incidence of pneumonia among the vaccinated and unvaccinated were kept during a period of some months. Wright in his report of the work thinks that the prophylactic vaccination was effective in reducing the incidence of pneumonia among the natives during the first three months following inoculation. He was also able to treat with therapeutic vaccines quite a large number of natives after the development of the pneumonic process. His statistics of this procedure show practically no difference in the death-rate between the inoculated and uninoculated. This he does not regard as indicating the inefficiency of the method, because the doses used were small. Another series of cases, inoculated with what he considered the optimum dose, and at a time that might be considered within the incubation period of the disease, showed a lesser incidence and death-rate than the controls. Later reports of this work have failed to establish the efficacy of prophylactic vaccination in preventing the development of pneumonia, and indicate approximately as high an incidence among the inoculated as among the uninoculated. Recent work shows the existence of different races of pneumococcus from a serological standpoint as the infectious agent in pneumonia on the Rand, and, in the light of these studies, some improvement in the efficiency of the vaccine may be brought about by the use of special strains or strains to which the natives are exposed, factors that were not taken into account by Wright in his immunization experiments.

More recently Cecil and Austin vaccinated 12,519 soldiers against pneumococcus Types I, II, and III and after a short period of observation, ten weeks, noted no cases of pneumococcus Types I, II, and III pneumonias among the vaccinated, while there were 26 cases of these types of pneumonia among the unvaccinated. Experimentally Cecil and Steffen have shown that large doses of Type I pneumococcus vaccine subcutaneously and smaller doses intravenously will protect monkeys from Type I pneumonias when subjected to intratracheal inoculation of virulent Type I pneumococcus.

On the other hand McCoy, Hasseltine, Wadsworth, and Kirkbride report the results of the inoculation of 17,000 inmates of New York State Institutions with 18,000 controls and feel that the results did not admit any definite conclusions.

From this review, it is easily seen that the status of vaccination in pneumonia is still doubtful. In general, in infective processes associated with fever, science would forbid the use of such methods until it was determined whether or no the process represented a progressive undermining of the body resistance. In such conditions very small matters may influence the course of disease in an unfavorable manner, so that under such circumstances vaccination must be regarded as a highly experimental method, and should not be undertaken save under the advice of one trained in the problems of bacteriology and immunity. On the practical side the evidence of clinicians in favor of vaccination as a therapeutic measure in pneumonia is insufficient to overthrow the general scientific arguments against the procedure.

Leukocyte Extract

After consideration of the failure of immune sera and specific vaccines to influence favorably most diseases of infectious origin, Hiss directed his attention to the important rôle played by the phagocytes in bacterial infection. He came to the conclusion that in recovery from many diseases we are dealing with an immunity which is largely cellular in type, not only in the sense of phagocytosis and digestion of bacteria, but also in the neutralization of poisons set free by their disintegration, the neutralizing bodies being contained largely within the phagocytic cells mainly for their own protection and not usually set free for the advantage of the cell community at large. This idea stimulated him to attempt to aid the leukocytes in their battle with the invading microörganism by furnishing them as directly as possible with weapons to carry on the struggle successfully. These weapons, whatever might be their nature, he assumed might be furnished by an extract of the active substances of the leukocytes themselves, which were not ordinarily found free in the plasma. He considered that extracts would be more efficacious than living leukocytes themselves, since being diffusible they would probably be distributed impartially to all parts of the body and, as quickly as absorption would permit, relieve the fatigued leukocytes and protect, by any toxin-neutralizing or other power they might possess, the cells of highly specialized functions. The extracts were prepared largely from leukocytes obtained from rabbits, were thoroughly emulsified in distilled water, allowed to stand at 37.5° C. for a few hours and then kept on ice until used. The total product, including residue and supernatant fluid, was used for injection. In addition to a number of other infections, these products have been used in the treatment of experimental pneumococcus infections in animals and in lobar pneumonia in man.

The animal experiments cited as a basis for the rationality of this form of therapy seem to indicate a favorable influence of the extracts on pneumococcus infection. Hiss says that in animals treated with the extract of leukocytes from normal rabbits, an infection, surely fatal in untreated controls, becomes markedly modified in such treated animals, even if the treatment is delayed many hours. Out of 8 control animals used in four experiments, in which the dose of pneumococci was the same, all died, averaging only forty-five hours of life after being infected. Of the animals treated, some as late as twenty-four hours after infection, 9 out of 12 survived and 3 died with an average life of sixty hours after infection, 2 of which had not received treatment until after the expiration of twenty-four hours. A number of other experiments were performed in which the results were also favorable. On the other hand, living leukocytes, introduced either subcutaneously or intraperitoneally, had no noticeable effect on like infections.

Encouraged by the results of these experiments upon animals, a limited number of observers have tested the efficacy of leukocyte extract in the treatment of lobar pneumonia in man. In 7 cases so treated, reported by Hiss and Zinsser, they thought that they observed a favorable action of the extract on the temperature and general condition of the patient, and a tendency for the number of leukocytes in the blood to increase subsequent to the injections. The leukocyte extract was given subcutaneously either in single or repeated doses of 10 c.c. Floyd and Lucas have reported the treatment of 41 cases of pneumonia by the method of Hiss and Zinsser. Of these 41 cases, 5 died and 36 recovered, a mortality of 12 per cent. A comparison of 25 cases untreated with 25 treated cases shows a mortality more than double in the series of untreated cases as compared with the treated cases. Twelve of the cases were in children and in 29 the age ranged from twenty to seventy years. Their impressions were that in a number of cases the disease was appreciably shortened and with but few exceptions there was a noticeable improvement in the comfort and symptoms of the patient. In cases with severe toxemia, the effect of the injections was marked, and they feel that the agent may prove of considerable therapeutic value. The extract was given in doses of from 10 to 20 c.c., repeated from two to four times in twenty-four hours. In no instance did the treatments cause any ill effects.

Hiss in a later paper gives an extremely favorable report of the value of his method in the treatment of pneumonia. The total number of cases reported is 53. Of this number, 3 ended fatally, a mortality of 5.6 per cent. He says that the most obvious effects of the extract were an almost immediate improvement in the feeling of well-being of the patient, a beneficial change in the quality of the circulation and a reduction of the pulse rate. In some instances the crisis was early, and in others the temperature fall was by lysis. The spreading of the lesion was usually halted and the convalescence rapid and uninterrupted. One of the most notable effects was the increase in the leukocytosis that followed the treatments. His general conclusion is that in cases treated early the disease is rendered largely benign, and the course markedly shortened. In this series of cases the doses of extract employed were very much larger than those used previously, varying from 20 to 60 c.c. repeated every four hours.

In spite of the very favorable reports of the few observers who have undertaken to treat pneumonia by this method, it has not as yet received any wide application. From a theoretical standpoint it represents an attempt to supply a deficiency of a type of immune bodies which most observers believe to exist, and of which the importance is no doubt very great. Of their nature or mode of action, however, we know very little, and whether, when passed from one animal to another by means of artificial preparations, they are still effective may well be questioned. The work of Hiss indicates that this may be so, and from the clinical cases it would seem that the leukocytic substances of lower animals can stimulate a considerable degree of leukocytosis in man. The work deserves and requires further study before the results reported can be generally accepted.

CHEMOTHERAPY

To Morgenroth and his assistants we owe the first progress that has been made so far in the attempt to control pneumococcus infection by means of a chemical compound with specific action. Because of the reports of the possible action of quinin in pneumonia, they used this alkaloid and substances closely related as a basis for their experimental observations on the effect of these substances on the course of experimental pneumococcus infections in animals. Morgenroth and Halberstaedter had previously found that certain quinin derivatives were useful in the treatment of experimental trypanosomiasis and, because of certain characteristics which trypanosomes have in common with the pneumococcus, decided to test the efficiency of these bodies in pneumococcus infections. A number of derivatives, quinin, hydrochinin, hydroclorisochinin, ethylhydrocuprein, and propylhydrocuprein, were employed in the experiments. The first positive results were obtained by Morgenroth and Levy by the use of ethylhydrocuprein. In their first experiments they employed a 25 per cent watery solution of the drug and found, when this was injected into mice previous to injection of the infecting dose of pneumococcus, that, whereas all the controls died, one-quarter of treated animals survived. This result is very striking, as virulent pneumococci injected into mice kill these animals with unfailing regularity. In curative experiments in animals injected with ethylhydrocuprein six hours after infection, 50 per cent of the animals survived the controls. Under such conditions the administration of the drug undoubtedly effected a sterilization of the blood of the treated animals, inasmuch as, in mice at such a period after infection with pneumococcus, septicemia has already developed. The drug was active not only against a single strain of pneumococcus, but also against many other strains of typical pneumococci.

Further studies by Morgenroth and his associates showed that, by modifying the technic of administration of the drug, still better results could be obtained. The toxic dose of this substance is but little above its curative dose. Injection of water solution allowed rapid absorption and this was not desired, as Morgenroth had shown that its action on the pneumococcus was best when it was continued for some hours. In order to obtain a like form of action in animals, the free alkaloidal base was injected in an oily suspension from which the rate of absorption was slow. When this was done, prophylactic experiments gave from 80 to 100 per cent of survivals. In curative experiments the results were likewise improved by giving the drug in the same manner and repeating the dose every twenty-four hours for a few days.

Boehncke has tested in animals the therapeutic activity of the drug when given in combination with antipneumococcus serum. Both in prophylactic and curative experiments the results were favorable, although the serum and drug were both used in quantities which of themselves were insufficient to bring about a favorable result. It is noteworthy that the disinfecting action of ethylhydrocuprein does not seem to be inhibited by the action of serum, as is the case in many such compounds. Boehncke found that in infections where he used mixtures of typical and atypical pneumococci, by repeated injections of the mixtures beneficial effects were observed, although the serum alone was completely inactive against the atypical races. Small doses of ethylhydrocuprein seemed to increase very much the efficiency of the antipneumococcus serum.

Moore in this country has carried on an extensive investigation of the action of ethylhydrocuprein or optochin, as it is more commonly called, against the pneumococcus. He has tested the bactericidal action of the drug *in vitro* against the different biological groups of pneumococcus and finds that it is equally active against all types, but that it possesses no such specific action against streptococcus. This investigator has also found that the blood of rabbits, after the administration of optochin, acquires bactericidal powers for pneumococcus. The best results are obtained by subcutaneous injection. It is somewhat less active in rabbits when given intramuscularly, and seems to exert no activity when administered by mouth. In order to obtain satisfactory effects by the intravenous route, it was necessary to give the drug in toxic amounts. Moore has also found that the blood serum of man becomes bactericidal for pneumococcus after the administration of 0.5 gm. of optochin by mouth or subcutaneously. When given subcutaneously, the drug is very irritating and may produce necrosis with the formation of a sluggish ulcer. He has also tested the value of combining optochin with specific antipneumococcus serum in the treatment of pneumococcus infection in animals, and finds that doses of optochin, which in themselves are so small as to have no therapeutic value, enhance many times the protective value of threshold doses of antipneumococcus serum.

Parallel with the experimental work in animals on the efficiency of ethylhydrocuprein, observations on the efficiency of ethylhydrocuprein in the treatment of pneumonia in man have been carried on. Fraenkel thinks that the drug is not yet suitable for human application, inasmuch as it has not a clear-cut action in a large proportion of cases. Wright was unable to observe any therapeutic effects whatever. Unfortunately the toxic dose of the drug is so near the therapeutic dose that great care has to be taken in its use. Both noted several instances of amblyopia following its administration. Though the sight is recovered, it is possible that in some cases permanent blindness might result. According to Fraenkel the effects of the drug on the course of the disease were as follows: In all, 21 cases of pneumonia were treated with ethylhydrocuprein; in 9 of the cases treated, 43 per cent, there was no noticeable change following the exhibition of the drug; in 6 cases, 28.5 per cent, a doubtful result; and in 6 more cases, 28.5 per cent, a rather marked beneficial action. In the 6 cases in which the drug seemed to show some beneficial influence on the course of the pneumonic process, the temperature dropped on from the fourth to the fifth day. In 4 of the cases the temperature fell within twelve hours after the administration of the drug and in 2 it fell by lysis. The general character of the cases studied at this time was mild, and most of the patients recovered spontaneously.

Parkinson has treated 9 cases of pneumonia with ethylhydrocuprein. Three of the cases had crises somewhat earlier than usual, the fourth to fifth day, but inasmuch as such early crises are not unusual, definite deductions cannot be drawn from them. Two patients died and in the remaining 4 the drug had no noticeable effect. Two of these later developed empyema. There was a slight rise in temperature following treatment in some of the cases, but no noteworthy effect on the pulse or respiration. In 3 cases out of the 9 treated, the pupils became widely dilated, but there were no instances of amblyopia. His conclusions are that ethylhydrocuprein has no effect on pneumonia in man, and that toxic symptoms may appear after the administration of 1 gm. by mouth or 0.5 gm. hypodermically.

Baermann has recently reported the treatment of 31 cases of pneumonia with ethylhydrocuprein, in some instances combined with serum obtained from patients convalescent from pneumonia. Of 5 cases treated by intramuscular injections of the ethylhydrocuprein base suspended in oil, favorable results were obtained in 3 cases, and 2 died. One of these latter had pneumococci in the blood and it is possible that the drug caused some diminution in their numbers. These patients all received repeated doses of 0.5 gm. ethylhydrocuprein suspended in oil, and no toxic effects are mentioned. Seven cases were treated with ethylhydrocuprein hydrochlorid by mouth in repeated doses of 0.25 gm. to 0.5 gm. No amblyopia was noted. Six of the patients so treated recovered and seemed to derive benefit from the use of the drug, and 1 died. Nineteen cases were treated by combinations of serum from convalescent patients and ethylhydrocuprein. In some the drug was given intramuscularly in oil suspension, and in others by mouth. Four of these cases died, and in the others the treatment in general seemed to be beneficial. In some instances pneumococci were found in the blood, and these either disappeared or diminished in numbers after the treatments. Baermann thinks that the drug has an unmistakable curative action in pneumonia and looks forward to further observations of its action, especially when combined with immune serum. His results seem to be distinctly better than those previously obtained, and may in part be due to better methods of administration.

The occurrence of the European War has delayed any increase in the general experience of the value of optochin as a method for treating lobar pneumonia. However, the drug has been rather widely used in Germany and a summary of the results obtained has recently been published by Leschke. The cases are divided into two groups: those treated before the third day of the disease and those treated after the third day. In the 204 cases treated before the third day, the mortality was 5 per cent, and in the 119 cases treated after the third day was 20 per cent. The mortality for the total 323 cases was 11 per cent, which represents a considerable reduction in mortality from that ordinarily observed. Moore and Chesney have recently made a very careful study of the effect of optochin in lobar pneumonia, and also give a summary of the total number of treated cases up to the present time. In order to obtain an accurate knowledge of the use and effect of the drug, recourse should be had to the original article. These investigators recommend a dosage of the drug, based on body weight, of from 0.024 to 0.026 gm. per kg., which is the amount necessary to insure bactericidal development by the blood serum of the individual under treatment. An initial dose of 0.45 gm. is given and the remainder divided into small doses of 0.15 gm. given at from two to three-hour intervals. The advantage of this method is that the bactericidal power of the blood rises rapidly and is maintained at a fairly constant level throughout the course of treatment. The administration of the drug is continued for about twenty-four hours after the temperature has fallen.

Optochin in certain individuals gives rise to toxic symptoms which constitute a distinct disadvantage in its use. The margin of safety is rather narrow and great care must be taken to avoid too large doses. The toxic effects seem to depend somewhat upon too great a concentration of the drug in the blood at one time and this is the reason for the repeated small doses, since when 0.5 gm. doses are given the concentration rises rapidly and generally falls considerably before the time for the next dose. Optochin, like quinin, exhibits its chief toxic action against the special senses. Deafness not infrequently occurs during treatment, but recovery seems to be complete, and this is not necessarily regarded as an indication for the cessation of treatment. The effect of optochin on the eye, when given in toxic doses, is much more serious, and the administration of the drug should not be continued after the appearance of eye symptoms. These consist of widening of the pupil with failure to react to light, dimness of vision, and in some instances complete blindness. In extreme cases the eye grounds show pallor of the retina with marked narrowing of the vessels. Complete blindness may persist for a week or more, with gradual return of vision. In many instances recovery is complete, but in some there is apparently permanent damage to the retina so that although central vision is normal, there is marked contraction of the visual fields. In only one instance so far reported has blindness been permanent, a case in which a very large dosage of the drug was employed. Toxic eye symptoms, however, may develop after a comparatively small total dosage, 2.0 gm. in 0.5 gm. doses in one instance. It is to be expected that optochin will receive a wide application although Moore and Chesney, in view of the toxic effects of the drug, did not think their series justified its further use.

Recent investigations conducted by Lamar, though they do not belong to the field of specific chemotherapy, may be mentioned under this heading. The studies have in view the development of a method applicable to the treatment of localized pneumococcus infections, such as pneumococcus meningitis or arthritis. It was pointed out by Neufeld some years ago that the pneumococcus is soluble in bile, very small amounts causing its complete disappearance. Certain other substances, whose physical action is much like that of bile, are known to exist. The most important of these are the unsaturated fatty acids. The soluble soaps of these acids, especially that of oleic acid, possess like bile the quality of dissolving pneumococci. Moreover, when pneumococci are exposed to their action, even in great dilution, they subsequently undergo autolysis much more rapidly and completely than organisms not so treated. Such soaped pneumococci when exposed to the action of normal serum disintegrate, but a few always remain and subsequently show active growth. On the other hand, when they are placed in antipneumococcus serum, the destruction is complete. The action of the serum is specific and shows no action against atypical strains that have been treated with oleate. It is known that considerable quantities of the unsaturated fatty acids exist in the animal cell, and are set free from the breaking down of the lecithin complexes when autolysis of tissue or resolution of lung occurs. The lytic action of these substances on pneumococcus is, however, suspended in the presence of protein-containing solutions, such as blood serum, so that their action in natural infection must be limited. Lamar was able to suspend the serum inhibition by adding to the soap serum mixtures an appropriate quantity of boric acid. Working with such mixtures he was able to obtain definitely beneficial results in local pneumococcus infections in animals. Infection could be prevented in small animals when the mixture was previously injected into the peritoneal cavity, infection following later in the same place. Therapeutic doses were also effective provided they were not given too long after infection had occurred. In a series of experimental pneumococcic meningitis in monkeys, treatment with soap, serum and boric acid mixtures showed very encouraging results. Infections of the meninges are especially suited to this method of treatment, because of the low protein content of the spinal fluid. In a number of instances Lamar was able to sterilize the spinal fluid of monkeys that had been infected some hours previous to the administration of the first dose of the therapeutic mixture. So far this method of treatment has not received any extended application to local pneumococcus infections in man, though it would seem well worth trying in such a hopeless condition as pneumococcus meningitis.

It has been suggested in the past few years by the advocates of camphor in the treatment of pneumonia that this substance has a direct action on the pneumococci. Boehncke recently investigated this alleged action experimentally and found that he was able to protect animals against a fatal dose of pneumococci by treating them previously with varying doses of camphor in oil. He was unable to confirm Welch's results on the therapeutic value of camphorated oil in rabbits when administered after infection had occurred. By means of large prophylactic doses, however, he was able to protect rabbits against surely fatal doses even when given intravenously. As in the case of ethylhydrocuprein, camphor was used by Boehncke in combination with antipneumococcus serum. This method seemed to give better results than the administration of camphor alone. Camphor has been used, at times in large doses, for many years by physicians in the treatment of pneumonia, largely, it is true, as a circulatory stimulant, but it is likely that if it had any very marked specific action against the pneumococcus, this would have been noted.

Ulcus Serpens Cornea

Ulcus serpens cornea is one of the severest types of ulceration of the eye. The process tends to spread rapidly and may involve considerable portions of the cornea. The process begins as a yellowish-gray infiltration near the center of the cornea. Ulceration rapidly takes place, the advancing edge becomes undermined and raised, the disease extends at the same time into the depths, so that perforation may quickly occur. There is almost always hypopyon, large amounts of the cornea may be destroyed, and occasionally panophthalmitis results. When healing occurs, all degrees of impairment of vision may result.

In about 98 per cent of cases of ulcus serpens, the pneumococcus has been proven to be the etiological agent. As far as has been determined, the organisms found differ in no way from the varieties of pneumococcus causing lobar pneumonia in man. Römer has devoted a number of years to study of the specific therapy of this affection. Experimental work has shown that immune bodies, either when produced actively or introduced passively by means of injections of specific sera, penetrate the cornea as well as other parts of the body, although in greatly reduced concentration. With these results as a basis, Römer and others have treated ulcus serpens with antipneumococcus serum. In animals prophylactic injections have prevented subsequent experimental infection of the cornea with pneumococcus. Römer's serum has been largely used in the therapy of human cases. It is prepared by the immunization of different animals to strains of pneumococcus obtained from cases of ulcus serpens, using preferably organisms of high virulence. The results, on the whole, seem to have been reasonably satisfactory and there seems to have been improvement from year to year. In favorable cases there is a reaction in the ulcer following the injection of serum, and this is followed by resolution. The extent of the process is much limited, and the hypopyon in many instances clears up as well. In general, the amount of permanent damage is much less in serum-treated cases than in those that are untreated. Paul, in a series of observations extending over a number of years, has had favorable results from the use of serum in 55 per cent of his cases, and Gebb and Römer in from 71 to 80 per cent. The outcome is more favorable the earlier the case is treated. When the ulcer is well advanced, successful treatment becomes a much more difficult matter. Recently the best results have been obtained by the administration of a single large dose of antipneumococcus serum given either subcutaneously or intravenously. Although there have been a number of contradictory results, the weight of evidence indicates that antipneumococcus serum is a valuable aid in the treatment of ulcus serpens. As in pneumonia, the existence of different varieties of pneumococcus is probable, and the further adaptation of the serum to the types of pneumococcus concerned may increase its efficiency. In addition to the use of antipneumococcus serum alone, active immunization by means of vaccines, and a combined therapy using both vaccines and immune serum, have been employed in the treatment of ulcus serpens. Both methods have given some valuable results, especially the latter.

Since the introduction by Morgenroth of optochin into the therapy of pneumococcus infections, this drug has been used extensively in Germany in the treatment of ulcus serpens. Most of the investigators report satisfactory results from its application. A 1 to 2 per cent water solution of the drug is applied locally and is said to result in unusually rapid healing of the ulcer. It causes no damage to the corneal epithelium in this dilution, and the burning sensation caused by its application can be obviated by the use of a local anesthetic. Pneumococcus ulcer of the cornea usually results in considerable destruction of tissue with scar formation. Treatment with optochin is said to give a more satisfactory end result as far as permanent damage to the cornea is concerned than any of the methods hitherto employed, especially those in which the cautery is used.[1]

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[1] Ophthalmologists in this country report distinctly favorable results from the treatment of pneumococcus ulcer of the cornea by local applications of optochin. —EDITORS (Billings and Irons).

SPECIFIC PROPHYLAXIS

Russell L. Cecil

The incidence rate of lobar penumonia in the United States is slowly rising year by year as the population becomes more and more concentrated in the cities and towns. Already the number of deaths from pneumonia exceeds that from tuberculosis. In 1920, one out of every ten deaths among policy holders of the Metropolitan Life Insurance Company was caused by pneumonia. The prevention of pneumonia is, therefore, one of the most important health problems of the day. Unfortunately the disease does not lend itself to control by ordinary hygienic and sanitary measures. Infection is transmitted by direct or indirect contact, most frequently by the droplet route; and as long as people congregate in public places and in public conveyances where close contact is inevitable, just so surely will pneumonia continue to menace the public health.

It would appear from these considerations that the greatest hope of preventing pneumonia lies in some method of artificial immunization. It has been only within the last few years. however, that any serious effort has been made along this line.

Lobar pneumonia is an acute infectious disease caused, in the great majority of cases, by the pneumococcus. Approximately 95 per cent of all cases of true lobar pneumonia are of pneumococcal origin. The streptococcus and Friedländer's bacillus are responsible for the few remaining cases. In this article our attention will be confined to the pneumococcus and to a consideration of pneumococcus immunity.

Immunity Following Lobar Pneumonia.—The tendency of certain individuals to repeated attacks of pneumonia has at times given rise to doubt whether there exists such a thing as an acquired immunity to pneumonia; yet considerable evidence can be brought forward to show that a rather high degree of immunity to the pneumococcus follows an attack of pneumonia. The crisis itself is a striking expression of immunity. Furthermore, Dochez has shown that the serum of patients convalescing from pneumonia usually contains protective substances against the homologous type of pneumococcus, and Blake has demonstrated precipitins in the serum of cases of pneumonia that terminate favorably. In addition to these clinical studies, accurate information on the subject of immunity following pneumonia has been obtained from experimental work on animals.

In some recently reported studies Cecil and Blake have shown that in monkeys an attack of pneumococcus Type I pneumonia protects the animals completely against a second infection by the homologous type. The duration of this immunity was not determined, but it probably exists for several months at least. Moreover, a certain amount of cross immunity against the other fixed types of pneumococcus is usually demonstrable in monkeys that have recovered from pneumonia. While it is true that certain persons show a susceptibility to repeated attacks of pneumonia, these attacks rarely come at intervals of less than one year. In view of this and other evidence it appears probable that one attack of pneumococcus pneumonia confers enough immunity to protect the patient for at least one year. In this respect pneumonia differs from typhoid fever, an attack of which usually confers a lifelong immunity. Typhoid vaccine, however, protects for only a comparatively short time.

Active Immunization against Pneumococcus.—A. Fränkel made the fundamental observation that rabbits inoculated with living, virulent pneumococci showed a high immunity if they recovered from the infection. G. and F. Klemperer produced active immunity in rabbits against pneumococcus in several different ways. They inoculated animals with heated pneumonic sputum, with pus from a pneumococcus empyema, and with cultures of pneumococcus which had been heated for one hour at 60° C. Emmerick injected rabbits with cultures which produced marked emaciation in the rabbits but did not kill them. By this method he produced a very high immunity, the animals withstanding 20 to 30 c.c. of highly virulent culture intravenously. These and other investigators have shown that an adequate immunity against pneumococcus infection can be developed in animals. Neufeld produced a high immunity in rabbits by subcutaneous and intravenous injections of killed pneumococci. He found, however, that it was necessary to use a virulent culture. Levy and Aoki have immunized animals with pneumococci killed by phenol and also with sensitized pneumococci.

It is clear from this brief review of the literature that the pneumococcus differs in no way from the great majority of other pathogenic bacteria in its capacity to stimulate artificial immunity in animals.

Active Immunization against Experimental Pneumonia.—In spite of careful studies on pneumococcus immunity by the earlier German investigators, no effort was made to study active immunity against pneumonia itself. In 1904, Wadsworth undertook to produce an active immunity against experimental pneumonia in rabbits. Wadsworth injected rabbits intratracheally with virulent pneumococci and thereby excited a patchy form of pneumonia. He then vaccinated normal rabbits with a saline suspension of pneumococci dissolved in rabbit bile. The immunized rabbits were subsequently injected intratracheally with 1 c.c. of an extremely virulent culture of pneumococcus. Of the 11 immunized animals none died, but a few were seriously ill for 24 to 36 hours. When killed the rabbits showed areas of diffuse consolidation involving considerable parts of the lung. Of the 5 control rabbits, 3 died without lung lesions; the 2 others lived a few days longer and showed at autopsy small areas of consolidation in the lungs. It is evident from these experiments that Wadsworth produced a partial immunity in rabbits against pneumococcus infection. His infecting dose, however, was too large for the amount of immunity produced.

In 1920, Cecil and Blake studied the effect of prophylactic vaccination against experimental pneumococcus pneumonia in monkeys. They found that by injecting virulent pneumococci intratracheally in monkeys they could produce a typical lobar pneumonia which differed in no respect, clinically or pathologically, from pneumococcus pneumonia in man. In their vaccination experiments, small doses of pneumococcus lipovaccine were used and each monkey received one inoculation subcutaneously. By this method of vaccination partial immunity against pneumococcus was established, but not enough to prevent mild infections in the lungs. In a later study on monkeys, Cecil and Blake found that the subcutaneous injection of a small dose of living virulent pneumococci produced a high degree of active immunity sufficient to protect the animals completely against experimental pneumonia of the homologous type. Living cultures also stimulated a certain amount of cross immunity against other types of pneumonia which, however, varied considerably with individual monkeys. Vaccination with living virulent pneumococci caused severe, at times fatal, reactions in some of the monkeys, while in others the reactions were very mild.

Cecil and Steffen continued the study of active immunity against pneumococcus pneumonia in monkeys and found that the subcutaneous inoculation of monkeys with three large doses of pneumococcus Type I saline vaccine conferred upon them a complete immunity against experimental pneumococcus Type I pneumonia. They also found that the intravenous inoculation of small doses of pneumococcus Type I vaccine conferred complete immunity against the homologous type of pneumonia.

Active Immunization against Pneumonia in Man.—In spite of numerous theoretical studies on pneumococcus immunity, no efforts had been made to vaccinate human beings against pneumonia until 1911, when Sir Almroth Wright undertook to immunize the workers in the diamond mines of South Africa against this disease. At that time pneumonia was a very frequent infection among the miners and the death-rate was quite high.

Wright vaccinated several thousand of the miners and studied the incidence of pneumonia among the vaccinated men for six months to one year after inoculation. A similar record was kept of the incidence of pneumonia among unvaccinated miners. Wright's treatment consisted in the subcutaneous administration of one dose of pneumococcus vaccine containing 1,000,000,000 killed bacteria. Wright was convinced from his study that the incidence of pneumonia was considerably reduced during the first three months following inoculation. Later reports, however, of this work failed to establish the efficacy of his method of vaccination against pneumonia. His failure was probably due to two things: (1) at the time his experiment was conducted the various types of pneumococcus had not been differentiated; (2) the dosage he employed was much too small.

In 1913, Dochez and Gillespie published a classification of pneumococci and Lister independently reported shortly afterwards a similar classification of the pneumococci encountered in South Africa. Lister then undertook an experimental study of prophylactic inoculation against the various types of pneumococci in animals and man. He demonstrated that immunity could be produced in man against at least certain ones of these types either by subcutaneous inoculation or intravenous injection, more readily by the latter. He found that subcutaneous inoculation of 40,000,000,000 cocci of the strains he employed caused little if any toxic reaction in the guinea pig, rabbit, or man, and intravenous inoculation of 20,000,000,000 in the rabbit and 40,000,000,000 in man gave rise to but slight toxic reaction. On the basis of these experiments Lister undertook the prophylactic inoculation of large groups of miners against pneumonia. He at first advocated inoculation at seven-day intervals, each dose to consist of 6,000,000,000 cocci of each type against which immunity was desired. Subsequently he greatly reduced this dosage and gave three subcutaneous inoculations at seven-day intervals, each injection consisting of 2,000,000,000 of each type.

The workers in three different mines, the Crown, Premier Diamond, and De Beers Diamond, were inoculated with a vaccine composed of the three types of pneumococcus which were most prevalent in these mines. They were known as Types A, B, and C. Types B and C correspond to Types II and I respectively in Dochez and Gillespie's classification. Type A has not been encountered in America. In the De Beers Diamond Mine a fourth group was added, called Type H. In the De Beers experiment, 1,000,000,000 of Type H was added to each injection, making a total dosage at each injection of 7,000,000,000. The vaccinated miners were then observed over a period of six to twelve months, and in all three mines a definite decrease in the incidence and mortality rate of pneumonia was observed. In the case of the Crown Mines, every case of pneumonia which occurred among the vaccinated individuals was studied bacteriologically and the type of pneumococcus determined. No cases of the types against which the men had been vaccinated (Types A, B, and C) developed during the nine months of observation. Lister contends that this fact, namely, the alteration of a relative group prevalence by means of specific group inoculation, is a more critical test of the efficacy of pneumonia prophylaxis than the simultaneous comparison of pneumonia rates in inoculated and uninoculated (control) groups when the comparison is based upon the erroneous assumption that all cases of disease due to the pneumococcus are bacteriologically indistinguishable. He emphasizes the probability that the protection of a considerable part of the community by inoculation lessens the number of carriers, and perhaps the virulence of the strains found in the community, and, hence, confers a definite benefit upon the uninoculated group which would affect the use of this group as controls in a statistical sense. Lister reported no unpleasant effects from the vaccine.

In 1918, Cecil and Austin vaccinated 12,519 recruits against pneumonia at Camp Upton, New York. The vaccine was prepared from glucose broth cultures and consisted of equal parts of pneumococcus Types I, II and III. The pneumococci were separated from the broth by centrifugalization and heated to 55° C. for one hour. Three subcutaneous inoculations were given each man at intervals of from five to seven days. A few of the men received four inoculations. The dosage was as follows:

1st dose—3,000,000,000 pneumococci	1,000,000,000	Type I
	1,000,000,000	Type II
	1,000,000,000	Type III
2d dose—6,000,000,000 pneumococci	2,000,000,000	Type I
	2,000,000,000	Type II
	2,000,000,000	Type III
3d dose—9,000,000,000 pneumococci	3,000,000,000	Type I
	3,000,000,000	Type II
	3,000,000,000	Type III

These rather large doses were decided upon after experiments which seemed to indicate that large doses produced more protective substance in the patient's serum than small doses. The local and general reactions following the inoculations of pneumococcus vaccine varied greatly in different individuals, but in most cases were not severe. A few patients developed, at the site of inoculation, small sterile abscesses which were probably due to the direct action of the pneumococcus toxin on the tissue. The patients who showed these lesions exhibited sharp local reactions to each dose of vaccine, and this gave rise to the idea that the sterile abscesses might be an expression of bacterial anaphylaxis (Arthus' phenomenon).

The vaccinated troops were under observation for ten weeks following the inoculations. During that time no cases of pneumonia of the three fixed types occurred among the men who had received two or more injections of vaccine. In a control group of approximately 20,000 men there were 26 cases of pneumococcus Types I, II and III pneumonia during the same period. Strangely enough the incidence of pneumococcus Type IV pneumonia and streptococcus pneumonia was also much lower among the vaccinated troops than among the unvaccinated.

The following winter, Cecil and Vaughan conducted a second experiment with pneumococcus vaccine at Camp Wheeler, Georgia. On this occasion 13,460 men, about 80 per cent of the entire camp strength, were vaccinated against pneumonia with a pneumococcus vaccine containing 10,000,000,000 each of pneumococcus Types I, II and III in each cubic centimeter of vaccine. In this experiment, however, the pneumococci were suspended in cotton-seed oil instead of the usual salt solution. Each soldier received a single injection subcutaneously. The dose was 1 c.c. of the lipovaccine, equivalent to 30,000,000,000 pneumococci. Conditions at Camp Wheeler were not nearly so favorable for testing the value of pneumococcus vaccine as they had been at Camp Upton. The pandemic of influenza swept over the camp in the midst of the experiment and, because of the lowered resistance which the influenza virus induced, a certain amount of pneumonia of all types developed among the vaccinated men. Furthermore, the pneumonia, which accompanied the influenza epidemic was due in great part to Type IV pneumococcus and streptococcus, neither of which organisms had been included in the vaccine. The results obtained at Camp Wheeler, while not so successful as those at Camp Upton, were, nevertheless, quite encouraging. Four-fifths of the population was vaccinated, but almost as many cases of pneumonia developed among the unvaccinated one-fifth as occurred among the entire vaccinated four-fifths of camp. Reckoning from one week after vaccination, the time when the individual's immunity begins to develop, only eight cases of Types I, II and III pneumonia occurred among the vaccinated men and all those were secondary to severe attacks of influenza. Using the same standard, 124 cases of Type IV pneumonia developed among the vaccinated troops and 103 of these were secondary to influenza. Reckoning from the day of vaccination, there were 33 cases of pneumococcus Types I, II and III pneumonia among the vaccinated four-fifths of the camp and 42 cases of pneumonia of these types among the unvaccinated one-fifth at camp. The death-rate for 155 cases of pneumonia, including all types that developed among vaccinated troops one week or more after vaccination, was only 12.2 per cent, whereas the death-rate for 327 cases of all types that occurred among unvaccinated troops was 22.3 per cent.

The author believes that even better results would have been obtained at Camp Wheeler, if a saline vaccine similar to that used at Camp Upton had been employed instead of the lipovaccine. Experiments on animals have conclusively shown that bacteria suspended in oil do not possess as potent an antigenic capacity as when suspended in salt solution. In fact, lipovaccine has so many disadvantages that at the present time the

Hygienic Laboratory of the United States Public Health Service will not issue licenses for its manufacture.

During the winter and early spring of 1919 pneumococcus vaccine was used extensively in the United States Army, both in the training camps and in the A.E.F. The following memorandum from the Surgeon General's Office in Washington is quoted from the official report of the Camp Surgeon at Camp Taylor, Kentucky:

> "January 28, 1919.
>
> "Our records show that of the 4,754 men who took pneumonia vaccine only 1 case of pneumonia has developed, while in the rest of the camp there have been over 80 cases. These figures require no further elaboration and it is recommended that the inoculation be made compulsory."

Another memorandum was submitted to the Surgeon General's Office in April, 1919, by Major Fred M. Meader, Medical Corps, showing results of vaccination against pneumonia in Base Section No. 2, A.E.F. In the following table, cases were not counted unless they developed seven days after vaccination.

Results of Vaccination against Pneumonia

Rate	Number of Men		Number of Pneumonia Cases		Deaths	
	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated
	45,849	49,463	38	83	5	11
Per 100,000	.....	.....	83.5	168	10.8	22.5

It will be seen from this table that both the incidence-rate and the death-rate were twice as high in the unvaccinated as in the vaccinated series.

In 1919, Major Borel of the French Medical Corps made a favorable report on the use of pneumococcus vaccine among the colored troops in the French Army. It seems that these troops, coming as they did from the tropical colonies, were very susceptible to pneumonia when they reached France. In one experiment three battalions were vaccinated and three other battalions were used as a control. The vaccine was composed of killed pneumococci suspended in normal salt solution in a concentration of 4,000,000,000 bacteria per cubic centimeter. The doses used were: (1) ½ c.c. (2,000,000,000 pneumococci); (2) 1 c.c. (4,000,000,000 pneumococci) eight days after the first injection. No reaction, either general or local, was observed among those vaccinated. The results obtained in this first experiment were very satisfactory, although the various types of pneumococci were not contained in the vaccine.

In a second experiment conducted by Major Borel, a pneumococcus vaccine composed of several types was prepared by Professor Nicolle at the Pasteur Institute, and 300 Sengalese were vaccinated with 3 subcutaneous injections (total—28,000,000,000 pneumococci) and 300 in the same organization were reserved for controls. The result was: 1 mild case of pneumonia and no deaths among the 300 vaccinated; 16 severe cases of pneumonia with 4 deaths among the unvaccinated controls. The troops were under observation two months after inoculation. The author concludes that pneumococcus vaccine is of great value and that its use should be continued.

Rosenow and Sturdivant vaccinated 8,306 inmates of institutions with a mixed vaccine consisting of pneumococci of the four types, hemolytic streptococcus, streptococcus viridans, and staphylococcus aureus. In the same experiment, 9,388 persons were not vaccinated and served as a control. The following table shows the results obtained:

Incidence-Rate Per 1,000 Persons

Groups	Total Number	Cases of Pneumonia	Deaths
Vaccinated 3 times.....	8,306	1.0	0.5
Not vaccinated.........	9,388	12.0	5.5

It will be seen from these figures that both the incidence-rate and the death-rate were materially decreased in the vaccinated series.

Von Sholly and Park vaccinated 1,536 persons in the employ of the Metropolitan Life Insurance Company with a mixed vaccine directed primarily against the milder respiratory infections. A control of 3,025 persons remained unvaccinated. This vaccine had practically no effect on the incidence of influenza and colds, the rate remaining about the same in both groups. The vaccine contained pneumococci of the three fixed types, streptococci, and influenza bacilli. The interesting feature of this experiment was that only 1 case of pneumonia developed among the 1,536 vaccinated employees, while 11 cases, or five times as many, occurred among the unvaccinated controls.

The only report on pneumococcus vaccine which has not been entirely favorable is that of McCoy, Hasseltine, Wadsworth and Kirkbride. These investigators studied the value of prophylactic vaccination against pneumonia among the inmates of certain New York State institutions. The vaccine used was a lipovaccine containing approximately 10,000,000,000 each of pneumococcus Types I, II and III. A single dose of 1 c.c. was administered subcutaneously to 17,752 patients, while 18,595 remained unvaccinated. The patients were under observation approximately two years, or rather during two pneumonia seasons. Among the vaccinated half, 253 cases of pneumonia developed, while 340 cases occurred among the uninoculated. Of these cases, only 122 in the vaccinated series and 186 in the control series were studied bacteriologically. An analysis of the bacteriological findings in this study is very interesting and possibly explains why more convincing results were not obtained. In the control series, only 23.6 per cent of the typed cases fell into the groups of pneumococci (Types I, II and III) against which the vaccine had been directed; 76.4 per cent of the cases being caused by other organisms—pneumococcus Type IV, streptococcus, B. Influenza, Friedländer's bacillus, etc. In the vaccinated series, only 18 per cent of the classified cases fell into the fixed types of pneumococcus. It should be noted further that, of the 22 cases of fixed type pneumonia that developed among the vaccinated patients, 16 were classified under pneumococcus Type III, the group which in civil life is most rarely encountered and which in animal experiments is the most difficult to immunize against. After making all allowances, however, it is noteworthy that, among 17,752 persons vaccinated against pneumonia and under observation for two years thereafter, there occurred only 1 case of pneumococcus Type I pneumonia, and only 2 cases of pneumococcus Type II pneumonia! Of course, there may have been a few more of these types among the unclassified cases. It is a well-known fact that the pneumonia which occurs in institutions for the insane, or, for that matter, in any institution, is nearly always of the bronchial type and presumably of streptococcus or pneumococcus Type IV origin. At Saranac Lake lobar pneumonia is practically never encountered in sanitariums for tuberculous patients. My criticism of this experiment, then, is that it was not a fair test for pneumococcus vaccine in that the vaccine was not directed against the type of pneumonia which was prevalent in these institutions.

Preparation of Pneumococcus Vaccine.—Pneumococcus vaccine is a suspension of killed pneumococci in normal salt solution. When the suspension is composed of a single strain of pneumococcus, the vaccine is "monovalent"; when the vaccine consists of several different strains, or types of pneumococcus, it is "polyvalent." Autogenous pneumococcus vaccine is usually monovalent; most of the stock pneumococcus vaccines on the market are polyvalent.

Pneumococci are cultivated for from eighteen to twenty-four hours on plain or glucose broth. The culture is then centrifuged, and the sediment of bacteria suspended in normal salt solution. Finally the saline suspension is heated at 55° C. for one-half hour to kill the pneumococci, and the vaccine standardized by the Wright method or by means of a nephelometer. Cultures are taken to test the sterility of the vaccine and tricresol is added to a concentration of 0.3 per cent as a preservative.

Method of Administration.—Pneumococcus vaccine is almost always administered subcutaneously. The proper method of giving the vaccine is to pinch up the skin, and insert the needle well under the dermis. Intracutaneous injections excite severe local reactions.

Pneumococcus vaccine, if injected intravenously, induces a sharp constitutional reaction (chill, fever, leukocytosis, etc.) similar to that following the intravenous injection of typhoid vaccine. This is the so-called "non-specific protein reaction," which follows the intravenous injection of any foreign protein, and is often employed in the treatment of certain forms of arthritis. Under ordinary circumstances, however, the intravenous injection of pneumococcus vaccine is strongly contra-indicated.

Dosage.—For therapeutic purposes, pneumococcus vaccine is administered in doses varying from 10,000,000 to 1,000,000,000 pneumococci or even more. For prophylaxis, much larger doses are used. The vaccine as prepared at the Army Medical School contained equal parts of pneumococcus Types I, II and III. In the United States Army, 3,000,000,000 to 9,000,000,000 was the dose of saline vaccine; 30,000,000,000 to 40,000,000,000 of the lipovaccine. In the case of saline vaccine, three injections were given at seven-day intervals; the first dose, 3,000,000,000; the second, 6,000,000,000; and the third, 9,000,000,000. In civil life we use a vaccine consisting of equal parts of pneumococcus Types I, II and III, suspended in salt solution, so that 1 c.c. contains a total of 9,000,000,000 killed bacteria. Three injections are given, separated by intervals of one week, as follows:

1st injection—0.3 c.c.—3,000,000,000.
2d injection—0.6 c.c.—6,000,000,000.
3d injection—1. c.c.—9,000,000,000.

Reactions.—Both the local and general reactions vary greatly in different individuals. The smaller the dose the milder the reaction. It is, therefore, desirable, if circumstances permit, to divide the total dosage (18,000,000,000) into five or six inoculations. It should always be remembered, however, that, within certain limits, the larger the total dose the higher will be the immunity conferred.

In general, it may be said that reactions to pneumococcus vaccine are similar to those following injections of typhoid vaccine. Within twenty-four hours after the injection an area of redness and induration appears at the site of inoculation, which is usually 2 or 3 cm. in diameter, but may be larger. Occasionally, small sterile infiltrations, which disappear spontaneously, follow the injection of large doses of pneumococcus vaccine. Such reactions appear to be an expression of cutaneous hypersusceptibility.

The constitutional reaction to pneumococcus vaccine is usually insignificant. In many cases it is entirely absent. In a small percentage of cases vaccination is followed by headache or backache, general malaise, chilly sensations and rise in temperature. These symptoms, however, are of short duration.

Indications for Use.—Prophylactic vaccination against pneumonia is indicated wherever large groups of individuals are living together under abnormal conditions. It is particularly valuable in the case of recruits in time of war and could be used with success on miners of all descriptions. Industrial workers who are exposed to the cold and wet, such as day laborers and truck drivers, chauffeurs, firemen and policemen, etc., may be vaccinated against pneumonia with great advantage. Nurses and attendants in hospitals are frequently exposed to pneumonia and should receive pneumococcus vaccine. Finally, there are certain people who are very susceptible to pneumonia and suffer from repeated attacks of the disease. During the past six or seven years the writer has vaccinated a number of such individuals and in no instance has the vaccine failed to give complete protection against a recurrence.

Contra-indications.—Pneumococcus vaccine should not be administered during an acute infection, and it is probably contra-indicated in chronic pulmonary tuberculosis. It should not be administered in large doses to patients with chronic cardiac or renal diseases or to pregnant women. It should not be administered during menstruation.

Intratracheal Vaccination against Pneumonia.—On account of the severe reaction sometimes produced by pneumococcus vaccine when injected subcutaneously, it is clear that improvements in the method of preparation and in the method of administration will have to be forthcoming before active immunization against pneumonia will be practical in civil life. During the past three years a number of modified pneumococcus vaccines have been tried by the author, but none of them has been quite so efficient in animal tests as the original saline suspension of killed pneumococci. With regard to modifications in the method of administration it seemed possible that a satisfactory immunity against pneumonia might be obtained by injecting the vaccine directly into the trachea. Such a procedure seems entirely rational, taking into consideration the fact that, in lobar pneumonia, infection takes place through the trachea and, in the very early stages, is a peritracheal and peribronchial infection. Monkeys were, therefore, inoculated intratracheally with three injections of ordinary pneumococcus Type I vaccine. The injections were given at intervals of five to seven days, and the immunity of the monkeys was tested two or three weeks after the third administration of vaccine by inoculating the immunized animals with small doses of living virulent pneumococcus culture. In these experiments it was found that the intratracheal injection of pneumococcus vaccine affords just as satisfactory an immunity against pneumonia as that induced by subcutaneous or intravenous injections. Indeed, the successful immunization of monkeys with three small intratracheal doses of vaccine indicates that immunity is more readily induced by the intratracheal route than by the subcutaneous route.

An attempt was also made to immunize monkeys against pneumonia by spraying them with pneumococcus vaccine. Complete immunity against pneumonia was not obtained by this method, probably because the monkeys offered a great deal of resistance to the treatment and because the spray was not continued over a sufficiently long period of time. It is quite likely that the daily inhalation of a pneumococcus vaccine spray would prevent completely the severer forms of lobar pneumonia in man. It is probable that the immunity established against pneumococcus by vaccination is of rather short duration, but with an atomizer the spray could be used frequently during the winter months and permanent immunity maintained in this way. Pneumonia will always be a difficult disease to control by sanitary or hygienic measures. It would seem that in the spray we may possess a simple and efficient method of eliminating the severe forms of the disease.

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CHAPTER XXX

EMPYEMA

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Definition.—Empyema, or pyothorax, is a collection of pus in the pleural cavity. The effusion is usually serous at first, then seropurulent and finally purulent. The pneumococcus and streptococcus are most often found in the exudate, and in a few the fluid is sterile. The last named are often of tubercular origin.

The majority of cases of empyema are met as sequels of lobar pneumonia, of bronchopneumonia, or of tuberculosis of the lungs. During the War empyema was a frequent and formidable complication of measles, streptococcus and influenza epidemics.

The pus developing after lobar pneumonia is thick and of a peculiar greenish-yellow color. The streptococcus and tuberculous pus is thinner, while that of actinomycosis is thick and filled with characteristic granules. A foul-smelling pus should lead one to suspect an infection with colon bacillus or Proteus vulgaris.

Prognosis.—A pleural abscess may be absorbed spontaneously. Such an event, however, is generally the result of perforation and drainage, either through the chest wall or through the lung and bronchial tubes. Exceptionally, the pus burrows down along the spine and emerges at the groin.

Pure infections of pneumococcus are the most favorable to recovery, while those of streptococcus origin are apt to be more prolonged and difficult to drain. Tuberculous and mixed infections are the least amenable to treatment.

The outlook for the empyema patient is largely determined by promptness of diagnosis and evacuation of the pus.

TREATMENT

Thoracentesis and aspiration have proved entirely inadequate for the treatment of empyema. A few clinicians still adhere to this procedure, because some cases, especially in childhood, recover after one or two evacuations with the trocar. There is no reasonable objection to the use of the trocar for diagnostic purposes in suspected empyema, and if pus is obtained it is often advisable to withdraw a portion of the exudate for temporary relief of symptoms. But the discovery of pus in the pleural cavity demands the same radical measures as an abscess in any other cavity of the body, namely, free opening and continuous drainage.

An attempt to carry off the pus by frequently repeated aspiration nearly always results in failure, and the surgeon is called in to operate at a time when the patient's vitality is reduced and the chance for recovery greatly impaired. Bülau devised a method by which permanent aspiration could be used after ordinary puncture. Upon the entrance of the trocar a small catheter is inserted through the cannula and allowed to remain while the cannula is withdrawn. The catheter is held in place by a collodion dressing and connected with a long tube leading to a vessel containing an antiseptic solution. Thus a continuous siphonage of pus is secured, which is gradual enough to favor a slow reëxpansion of the lung. This procedure is recommended by Rosenbach and Bohland whenever it seems inadvisable to subject the patient to a cutting operation or when the shock of sudden evacuation is feared. The disadvantages of the method are the likelihood of the catheter coming out as the patient moves or coughs, and the tendency of the small lumen to be obstructed by flakes of fibrin.

Military Experience.—In no branch of medicine or surgery did the World War bring about such an intensive study and yield more useful results than in the management of empyema.

The opportunity was without parallel. The epidemic of streptococcus infections of the respiratory tract during the fall of 1917, occurring in conjunction with an epidemic of measles, resulted in a vast number of cases of bronchopneumonia with pleural effusion abounding in streptococci and with streptococci in the blood-stream. The septic process was often so overwhelming that the lung had insufficient time to undergo consolidation. Neither aspiration nor surgical incision had any marked effect in checking the progress of the septicemia in many cases. Those who survived developed both consolidation of the lung and empyema and often abscess of the lung. At this stage surgical drainage was effective if all the pus pockets could be reached.

During the following winter the streptococcus epidemic continued, but ran a less stormy and virulent course. The lung consolidated and pus collections developed more slowly, both in the pleural cavity and in the lung. Metastatic abscesses in the pericardium, joints and skin were common. The results of surgery were better and the mortality fell appreciably.

By spring the infection had become a mild affair and though empyemas were common they were amenable to treatment.

In the great influenza epidemic of 1918 a similar variability in virulence and mortality could be seen. At the beginning the sepsis was so great that every measure employed to combat the pneumonia with its complicating empyema seemed futile. Gradually the virulence waned and drainage both by aspiration and incision yielded excellent results.

A survey of therapeutic procedures during the streptococcus and influenza epidemics reveals the following facts:

1. During the early and virulent periods of the epidemics the mortality was high, while during the late periods the virulence was lessened and the mortality low.
2. Consequently, whatever particular method was employed for treatment of empyemas in the early period, for example, aspiration or thoracotomy, was disappointing and often condemned. Likewise, whatever treatment was employed in the later, milder periods, seemed brilliant, effective and was praised. Thus there arose protagonists for and against aspiration; for and against thoracotomy; for and against irrigation.
3. After the smoke of controversy had cleared there was a final unanimity in favor of early aspiration and of postponing thoracotomy until the patient had passed the acute phase of septicemia and established a good resistance to the shock of operation.

Much was accomplished by the Empyema Commission in standardizing the treatment of these cases. The Commission laid down the following principles of procedure:

1. Avoidance of an open pneumothorax in the acute stage during an active pneumonia.
2. Early sterilization and obliteration of the cavity.
3. Maintenance of nutrition of the patient.

The most important contribution to the mechanics of thoracotomy was made by Graham, a member of the Commission. He demonstrated by experiments on animals and human beings that the danger of establishing a free opening in the chest is dependent on the relation of the size of the opening to the vital capacity of the lungs. For example, an opening of eight square inches in a person with a vital capacity of 3,700 c.c. is compatible with safety, but this ratio cannot be exceeded with safety. Now Graham reasons that in the acute stage of pneumonic infections the vital capacity is profoundly lowered as evidenced by cyanosis and dyspnea, and that, therefore, the lung cannot withstand the additional strain of even a small free opening. As the acute toxemia subsides, the vital capacity of the lungs increases and permits the incision with safety.

The sterilization and obliteration of the pus cavity should be carried out, according to the Commission, by means of irrigation with Dakin's solution (0.5 per cent neutral sodium hypochlorite). This has proved successful in disinfecting the pleural cavity. Quite as important is the breaking up and removal of the thick exudate which in streptococcal infections tends to encapsulate the compressed lung and to bring about a fibrosis. Dakin's solution, it is claimed, accomplishes this purpose in a remarkable manner. The increased expansion of the lung under this treatment leads to the hope that the more extensive intrathoracic operations, such as decortication, may be avoided.

Thoracotomy.—Thoracotomy, or incision of the chest wall, is in a general way more satisfactory than aspiration, and either alone or combined with rib resection is the practice followed by most surgeons in this country. By preference the opening is made in the fifth or sixth interspace from the anterior axillary line backward two inches or more. The incision should be large enough to admit two fingers, thereby facilitating the breaking down of fibrinous masses which might interfere with the outflow of the pus. Permanent drainage is secured by the insertion of two large rubber drainage tubes that are kept from slipping inward by the use of a safety pin and are held firmly in place by a snug dressing. No effort is made to aspirate the pus, but it is allowed to escape slowly into thick layers of gauze loosely applied to the chest and supported by a chest binder. Aspiration of the exudate is open to the objection that it favors the rapid development of pneumothorax and disturbs the pulmonary circulation and the respiration. The gradual entrance of air into the pleural space, however, is not an undesirable event. In fact, the sucking in of air with inspiration has the effect of maintaining a moderate positive pressure within the cavity and thereby helps to force out the fluid with each act of expiration. The respirations act in the manner of a pump which draws in a volume of air and displaces a corresponding quantity of fluid.

At first the dressings are quickly saturated with the copious discharge and need frequent renewals. In a short time the outflow becomes much smaller, and it is necessary to shorten the tubes so as to avoid contact with the advancing lung and diaphragm. As the discharge dries up and the wound fills in, the drainage tubes are replaced by tubes of smaller size until they can be dispensed with altogether. During this period a rise in temperature, chills, sweating, and increasing leukocytosis are sure signs of obstruction in the free exit of the pus, and require that the flow be reëstablished.

Some surgeons advise an opening as low down in the thorax as possible (the eighth or ninth interspace, midaxillary line), in order to obtain perfect drainage. Experience does not sanction such a site, for with a low incision the tubes soon are bent or obstructed by the rising diaphragm.

Resection of the Ribs.—This serves a double purpose of maintaining an opening adequate for thorough drainage and of procuring a contraction in the chest wall in long-standing cases where the lung cannot expand.

In children and some adults the spaces are so narrow that drainage tubes are with difficulty held in place, and smaller tubes than are desirable must be used. The excision of a portion of one rib is a simple operation and satisfactorily solves the problem of drainage, provided the lung retains its power of expansion.

When the lung, as a result of firm adhesions or of cirrhotic changes following long compression, is incapable of filling out again with air, simple drainage cannot effect a cure. As long as an open pleural space remains, suppuration will continue. For this situation resection of several ribs is indicated. *Estlander's operation* of removal of a few ribs, leaving the periosteum and intercostal muscles, is performed for the obliteration of a space of moderate size. The soft parts come in immediate contact with the lung, and the abscess cavity is filled in. Schede's operation is reserved for the most extensive and desperate cases. All the ribs are removed, as well as the intercostal muscles, so that only a flap of skin and superficial muscles remain to form a covering for the collapsed lung. These more formidable procedures are becoming less necessary as improvement takes place in the early diagnosis and treatment of empyema.

By many surgeons resection of one or more ribs is a routine practice in the treatment of empyema. But it should be emphasized that others customarily perform a *single incision* only and claim equally good results. Where an open space exists and the lung cannot expand there is no difference of opinion—resection of the ribs is universally decided upon.

Irrigation.—Irrigation of the pleural cavity is rarely necessary in pneumococcus infections. Statistics show that healing goes on more rapidly when irrigation is not employed.

Various antiseptic solutions have been enthusiastically commended, only to be later abandoned. From the use of carbolic acid and bichlorid of mercury several instances of poisoning are recorded. Salicylic acid, boric acid, normal salt, permanganate of potash, iodin, and formalin solutions have been successively popular. Dakin's solution, as previously stated, has been extensively used during the War and since, especially in streptococcus empyemas. Many surgeons are enthusiastic over its effects, while others still prefer the dry method.

The purpose of irrigation is to wash out shreds of fibrin or necrotic masses and to disinfect the pleural cavity. But the desirability of removing the flakes of fibrin is open to question. Rosenbach contends that the introduction of fluid separates the pleural surfaces and destroys the meshes of granulation or repair tissue. From this point of view the procedure actually retards healing. With regard to the idea of disinfecting the cavity with strong antiseptics, some authors have been rather too sanguine. The bacteria are not only in the fluid, but are so embedded in the fibrinous exudate as to be beyond the reach of antiseptics.

Accidents Occurring During Irrigation.—In practicing irrigation it is well to bear in mind that occasionally alarming or even fatal symptoms occur. Fainting attacks may come on as they do in thoracentesis. A complication that seems quite peculiar to irrigation is the onset of *convulsive seizures* which sometimes end in death (Auberne). In another group of cases *hemiplegia* occurs, which nearly always clears up in a few hours. Janeway observed such a transitory paralysis on two different occasions while injecting peroxid of hydrogen. In the case of Bouveret iodin was the solution used. Forgues recorded a similar accident while adjusting the drainage tube that had come in contact with the lung. Death has taken place during the procedure. Billings relates an experience with a child two years of age, from whose chest only three ounces of pus were withdrawn. Immediately after the injection of a 2 per cent solution of formalin in glycerin, marked dyspnea, rapid pulse, and cyanosis appeared and life was extinct within an hour in spite of treatment.

The conclusions of Lewis and the author as to the cause of these attacks have been partly set forth. We found that absorption of chemical poisons contained in the irrigating solutions ordinarily employed cannot explain the phenomenon, for it occurs also with non-toxic solutions. Neither is the change in pressure conditions within the thorax responsible, because often the amount injected is trivial. The cause is found in an irritation of the pleura by the antiseptic solution, which reflexly disturbs the whole arterial circulation and often the cardiac and respiratory centers. Iodin solution (Lugol's) was the least harmful. Hydrogen peroxid was more irritating, while formalin was frequently a menace to life.

In human beings with an old thick exudate from chronic empyema the pleura is usually covered over, so that these circulatory disturbances are fortunately rare. When, however, even a small surface of the pleura is exposed by displacement of fibrin there is an element of danger in the use of antiseptic solutions.

Maintenance of Nutrition.—Too little emphasis in the past has been given to maintaining the nutrition of the patient with empyema. R. D. Bell observed that in patients taking 1,500 to 1,700 calories per diem there was a loss of 21 gm. of nitrogen per diem in excess of that ingested by the body as food. Hence, to the burden of infection is added the factor of starvation. He advises a diet containing 3,300 to 3,500 calories.

Treatment of Special Forms of Empyema

Empyema Necessitatis.—This is a condition in which a neglected pleural abscess becomes localized and bulges out the skin over an interspace. The incision should, of course, be made over this point.

Bilateral Empyema.—Bilateral empyema demands special consideration, because thoracotomy cannot usually be performed with safety. The production of a one-sided pneumothorax, which is well tolerated with a normal lung on the opposite side, becomes most precarious when this lung is also handicapped by an empyema.

Aspiration of one side at a time is advisable. If one lung expands sufficiently under this treatment thoracotomy may be undertaken with great caution on one side, while the trocar is used for the other. The prognosis in these cases is grave.

Empyema in Children.—This runs a more favorable course than in adults, excepting in early infancy. During the first two years of life the mortality is very high.

According to Blaker, over 85 per cent of all cases in childhood are secondary to pneumonia and usually are due to pneumococcus, which is the most benign infection.

In the treatment one should remember that children do not bear the shock of operation as well as adults. Since the chest is smaller and the normal rate of respiration more rapid than in adults, pneumothorax causes a greater embarrassment to respiration. For this reason, if the exudate is large, the preliminary withdrawal of part of the pus by the trocar will modify the shock of subsequent incision. The trocar should be sharp in order to avoid too forcible a thrust against the chest. At the time of incision the wound should be partially closed by the fingers, so that the outflow will not be rapid. Where drainage is impeded by the narrowness of the interspace, excision of a rib should be readily resorted to, since the bone will completely regenerate.

Empyema Associated with Pulmonary Tuberculosis.—A great divergence of opinion exists in respect to the management of this condition. The conservatives point to the numerous cases in which operation for empyema has lighted up the lesions in the lung and even induced a miliary tuberculosis. They also cite instances of spontaneous improvement or even healing in the presence of exudate, both serous and purulent. They further claim that tuberculous empyema is in reality a "cold abscess," free from bacteria, from which toxins are not absorbed.

Other more radical clinicians believe that prompt drainage of tuberculous empyema will often save the patient's life, and that a large collection of pus is seldom absorbed, as often occurs in a serous effusion.

Bergeat opens the chest whenever the opposite lung is in good condition and the strength of the patient permits (Braun). Brewer prefers aspiration, because with incision the danger of mixed infection is to be feared. The invasion of other bacteria results in septicemia.

Empyema developing with advanced or terminal tuberculosis certainly need not be disturbed out of consideration for the patient's comfort.

Empyema Associated with Actinomycosis.—According to Lord, the process usually begins in the lung and affects the pleura secondarily, causing a serofibrinous or more often a purulent exudate. Perforation of the chest wall is a common incident. The diagnosis is made by finding in the pus small granules which show the characteristic threads and club-shaped bodies. In addition to the evacuation of the pus, massive doses of potassium iodid should be given. Five hundred grains a day may be prescribed for two or three days, and repeated at intervals of ten days.

Encapsulated Empyema.—The difficulty of accurately diagnosticating a small pocket of pus stands in the way of a satisfactory therapy. The pus collection may be walled off between the lung and chest wall or between the lobes or between the lower lobe and the diaphragm. Perforation of the pus into the lung and bronchi is a fortunate occurrence, but perforation through the diaphragm leads to peritonitis. If the exploratory needle can locate the pocket, thoracotomy and drainage are indicated.

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CHAPTER XXXI

GONOCOCCUS INFECTION

George Blumer

Custom has decreed that the local manifestations of gonorrhea shall be treated by the urologist, and the ocular manifestations by the ophthalmologist. There remain to be considered the metastatic manifestations of the disease, that is, those lesions which result from the invasion of the circulation by the gonococcus with or without its lodgment in local foci such as the joints, and the production of focal metastatic inflammation.

General Gonococcus Infection.—General septicemia due to the gonococcus is luckily of rare occurrence. When it does occur it may or may not be accompanied by endocarditis, which is more commonly present than absent. The symptoms which should lead to the suspicion of its presence are the development of high fever, often accompanied by chills and sweats, without evidence of any local complication of sufficient magnitude to account for the symptoms. With the fever, digestive disturbances, a rapid pulse, a secondary anemia, and not infrequently skin eruptions of a papular, petechial or erythematous nature often occur. Physical examination often shows little but the general appearances accompanying a severe infection, though a palpable spleen may be present. The diagnosis rests in the last analysis on blood cultures, and a mixture of equal parts of ordinary agar and blood from the patient is usually a satisfactory medium for the growth of the organism.

When cardiac complications are present, the diagnosis rests on a rapid, overacting heart, the occurrence of heart murmurs of the type and localization associated with the particular valve or valves involved, and the appearance of embolic manifestations either in the skin or the internal organs.

Prophylaxis.—It is well to bear in mind that in some instances the generalization of a gonococcus infection has directly followed injudicious treatment. The clumsy or careless use of instruments for irrigation may open up channels through which the gonococcus gains access to the circulation. Complications, especially prostatic complications, should be very carefully handled as the prostatic capillaries are particularly easy of access to the gonococcus. The patient should be warned against sexual indulgence before the urethritis has subsided and also against alcoholic indulgence. In women unusual care must be taken at the menstrual periods and during pregnancy.

Treatment.—The general treatment is the same whether cardiac complications are present or not.

Specific therapy in the form of gonococcus vaccine or of antigonococcus serum is generally conceded to be of no value. The recorded cases of recovery are so few that they are explicable on the basis of spontaneous recovery, which doubtless occurs occasionally in this as in other forms of sepsis with or without endocarditis.

Chemotherapy is likewise of very dubious value. Various antiseptics, particularly the colloidal silver salts, have been administered intravenously, but there is no convincing evidence of their value. The same may be said to be true of attempts to influence the sepsis by non-specific measures such as saline infusions and the intravenous administration of peptone.

Transfusion, on account of its apparent value in other general infections is worthy of trial, particularly in those patients in whom severe anemia is present.

General treatment should consist of absolute rest in bed, the copious administration of water, unless contra-indicated by circulatory complications, a soft, easily digested diet, provision for sleep, if necessary by the use of sedatives, and care of the bowels and skin.

GONORRHEAL ARTHRITIS

This is the most common metastatic manifestation of gonorrhea and may follow not only urethritis but also gonorrheal ophthalmia, and rectal and vulvovaginal infection. It is more frequent in patients who have had multiple attacks and is generally stated to occur more often in males than in females. A personal predisposition to arthritis probably plays some part in its development. The joint manifestations occur most frequently when the disease is in the acute or subacute stages or as an accompaniment of an exacerbation of a chronic gonorrheal process. Signs of active urethritis frequently cease at the onset of the joint manifestations.

The condition may manifest itself clinically as an arthralgia, in which pain without obvious local joint changes is the prominent feature; as an acute arthritis, usually serofibrinous but occasionally purulent; as a chronic arthritis, either associated with fluid (gonorrheal hydrops) or with deformity and perhaps ankylosis. The acute serofibrinous arthritis is the common type, the others being unusual.

Gonorrheal arthritis is to be differentiated from acute articular rheumatism, from the acute form of arthritis deformans, from acute gout and from other forms of infectious arthritis. The history of an attack of gonorrhea, the finding of active manifestations of the disease in the urethra or elsewhere and the demonstration of Gram-negative diplococci in smears from the suspected focus are the most valuable methods of diagnosis. Diagnosis is much more difficult in women and children on account of the frequent lack of history and the anatomical peculiarities of the disease in them. In men, too, when the disease accompanies the lighting up of some old hidden focus in the prostate or seminal vesicles, diagnosis may be very difficult and may demand all available technical aids. There is still doubt as to the value of the gonococcus complement fixation test in these cases though many observers claim that in arthritis it is of service. Occasionally gonococci can be demonstrated by smear or culture in fluid aspirated from the joint itself. This is rather exceptional, however.

Treatment.—The treatment of gonorrheal arthritis involves:

1. Constitutional treatment.
2. Treatment of the primary focus, if discoverable.
3. Local and general treatment of the arthritis.

Constitutional Treatment.—During the active stage of the disease the patient should be in bed, should be encouraged to drink fluids copiously and should be on an easily digestible diet of sufficient caloric value to maintain proper nourishment. The regular evacuation of the bowels should be attended to by enema or mild purgation. Sleep should be obtained by mild sedatives unless pain be severe enough to require the use of narcotics. Fresh air and sunlight will aid in maintaining the general health and the morale.

Treatment of the Primary Focus.—The local infection, if obvious, should be treated along the usual lines. Urethritis, prostatitis, vesiculitis, vulvovaginitis or ophthalmia should receive the appropriate local therapy in spite of the fact that such interference occasionally leads to exacerbations of the joint process. In acute prostatitis or vesiculitis or in gonorrheal disease of the female adnexa, surgical intervention may be demanded. In subacute or chronic prostatitis, massage, properly given, may be of value.

Local Treatment of the Arthritis.—In the acute stages the joints should be immobilized but, as the active signs abate, undue immobilization is to be avoided and gentle massage and passive motion should be used to prevent ankylosis. In suppurative cases incision, drainage and irrigation with bland solutions or with mild antiseptics are demanded. In the usual serofibrinous type aspiration of the joint under strict aseptic precautions may give relief, especially in cases where the effusion is large in amount. Various local applications such as lead and opium lotion or icthyol have been recommended. Gennerich claims that Bier's hyperemia is sometimes of distinct value. Baking or the prolonged application of hot compresses or the local hot-water bath may relieve pain. Local radiation is recommended by Braendle in the chronic cases. He uses deep radiation with a hard tube and a long focal distance, filtering the rays through an aluminum screen 1 mm. thick and treating each side of the joint with a half normal dose calculated by the Sabouraud-Noire method. A single treatment often suffices, but in resistant cases repetition may be necessary.

General treatment of the arthritis consists in the use of vaccines, sera or non-specific protein shock therapy.

The use of vaccines in this country is associated with the names of Cole and Meakins and E. E. Irons. At the present time stock, polyvalent vaccines are generally used as there are many different strains of gonococci and the identification of the particular strain present in a given infection is often a practical impossibility. The dosage is to be judged mainly by the reaction in a given case. In an average case a dosage of 5,000,000 bacteria is a proper initial dose and the vaccine may be repeated every five days with 5,000,000 increment in each succeeding dose. Doses as high as 400,000,000 bacteria have been employed. Male patients usually bear larger doses than women or children. If the reaction following the first dose is not severe, the plan mentioned above may be followed, but judgment must be exercised in each patient. Some observers advise a closer spacing than every five days, indeed vaccines may often be administered every other day without harmful results. Administration at intervals of over a week is undesirable on account of the possibility of anaphylactic phenomena.

Serum treatment is seldom used at the present time as experience seems to show that it is less efficacious than vaccine treatment.

Protein shock therapy has been employed to some extent in recent years, but it is doubtful whether it will ever be a popular procedure with the patient on account of the violent reactions which follow its use. Even death has occurred in debilitated patients.

The technic consists of the intramuscular or intravenous injection of pure protein such as albumose or of substances containing protein such as milk or the bodies of bacteria. On account of its availability antityphoid vaccine has been frequently used. From 5,000,000 to 250,000,000 typhoid bacilli may be administered intravenously in saline solution. It is well to begin with small doses, 5,000,000 to 10,000,000 bacteria, and regulate the subsequent dosage according to the severity of the initial reaction. Subacute and chronic arthritis is more frequently benefited than the acute form. Favorable results have been reported by Miller and Lusk, Cecil and others. The method should be used with great caution in patients with a previous history suggesting anaphylactic phenomena and in patients with pronounced hypertension; in the former symptoms of anaphylactic shock may supervene and in the latter the rise in blood-pressure which accompanies the reaction may be detrimental. Needless to say it should not be employed in extremely debilitated patients.

Gonorrheal Tenovaginitis and Bursitis

Inflammation of the tendon sheaths or bursæ in gonorrhea is usually an accompaniment of arthritis and involves tendon sheaths or bursæ in the immediate neighborhood of infected joints. Occasionally it occurs as an isolated phenomenon. The complication occurs in the same circumstances that favor arthritis. The tendon sheaths of the lower extremities are usually involved but occupational strain may lead to involvement of those of the upper extremities. Various bursæ may be implicated, those subject to trauma being the ones most likely to be affected. As in the joints, the usual signs of inflammation are present associated with disability of varying degree, dependent on the location of the lesion. The inflammatory exudate may be serous, serofibrinous or purulent. In the last case there may be constitutional symptoms.

Treatment.—The treatment is essentially the same as for gonorrheal arthritis. If a purulent exudate is present, which is rare, incision and drainage are demanded. In cases with serous or serofibrinous exudate, aspiration may be of value. Immobilization during the acute stages, treatment of the original focus, general hygienic measures, vaccines and the various forms of physical therapy suggested under Arthritis may be tried.

Gonorrheal Inflammation of Muscles and Tendons

Aside from muscle involvement in the immediate neighborhood of inflamed joints, it is rare to find localized myositis as a metastatic phenomenon in gonorrhea. Two types of myositis have been described, an indurative form and a suppurative form. The indurative form usually involves the muscles of the lower extremities, the thigh muscles especially, and causes pain and foci of local induration. Suppurative myositis may occur as single or multiple abscesses and is usually an accompaniment of gonococcus septicemia. The usual symptoms and signs of abscess are present.

Treatment.—In the indurative form, rest with local applications of heat or the Preissnitz compress is indicated. Sedatives may be necessary if pain is severe. Incision is not demanded. In the suppurative form incision and drainage are indicated.

Gonorrheal Bone Lesions

The most important manifestation of bone involvement in gonorrhea is the painful heel first described by Jacquet thirty years ago. The pathological lesion is a bony exostosis which forms on the inferior surface of the os calcis, usually at the tubercle. Baer was able to cultivate gonococci from such lesions. Young males are usually affected and the process is generally a bilateral one. Inasmuch as the body weight is thrown on the tubercle in walking, the chief complaint is pain. This the patient trys to avoid by walking on the toes, producing a characteristic gait. X-ray pictures are quite characteristic and the diagnosis is not difficult.

Treatment.—It is useless to temporize with medical treatment, especially as the condition frequently results in almost complete disability. Exposure of the exostoses by open incision and removal by chiseling generally results in permanent cure.

Gonorrheal osteomyelitis is of great rarity and demands the same treatment as osteomyelitis due to other organisms. Periostitis with involvement of the subperiosteal layers of bone is more common and involves the leg bones by choice. It may be almost painless or may result in severe osteoscopic pain. Incision and thorough curettage of the involved bone usually results in prompt and permanent cure.

Gonorrheal periostitis without bone involvement may occur, producing localized tender swellings over the area involved. Symptomatic treatment for the pain in the form of heat is usually all that is necessary, as the process generally subsides spontaneously.

Pulmonary Complications of Gonorrhea

These are practically always incidents in a general gonococcus infection and are quite rare. The lesions of the lung parenchyma are associated with emboli and take the form either of infarctions or of embolic pneumonia. In either case pleurisy may accompany the pulmonary lesion. The symptoms and signs do not differ from those of the same lesions when due to other organisms. The diagnosis may be difficult if the primary gonorrheal focus is hidden and the prognosis is naturally grave on account of the underlying general sepsis.

Treatment.—There is no specific treatment. The general management has already been discussed under General Gonococcal Infection. The treatment for the pulmonary lesions is the same as that for similar lesions due to other organisms and is discussed under the appropriate sections elsewhere in this work. The local focus of infection should be eradicated if possible.

Gonorrheal Disease of the Nervous System

The only common neurological complications of gonorrhea are the neuralgias which may occur in the neighborhood of gonorrheal foci, either primary or secondary. It is important to remember that sciatica not infrequently occurs late in the course of gonorrheal urethritis in males, particularly when the prostate and seminal vesicles are involved in the process. Sciatica of gonorrheal origin is much less common in women, though by no means unknown. In association with gonorrheal sepsis neuritis, myelitis and cerebral embolism may occur, but are uncommon.

Treatment.—In patients with sciatica associated with gonorrhea, a careful investigation of the urinary tract, particularly the prostate and seminal vesicles, is demanded. If prostatitis or vesiculitis is found to be present, massage, or even surgical intervention, may be needed to clean up the local focus. In the meantime the patient should receive general supportive and eliminative treatment and the local condition should be relieved by rest, hot applications and anodynes.

CHAPTER XXXII

STREPTOCOCCUS SORE-THROAT

Edwin H. Place

Synonyms.—Septic Sore-throat; Pseudomembranous Angina; Pseudodiphtheria.

Streptococcus infections are among the commonest in man, and many of them are of serious type. There is a great variety in the clinical manifestations, depending upon virulence, resistance, the location of the infection and possibly peculiarities of the strain. The causal relation of a distinctive type of streptococcus to any of these clinical varieties, however, remains to be proved. It is not, therefore, possible to say whether mild streptococcus tonsillar infections, such as common follicular tonsillitis, differ from the severer anginose infections in etiology or simply in the severity of the reaction. In widespread epidemics from a common milk-borne source, all degrees of severity occur. Because of lack of a fixed classification of the streptococci, as well as the frequency of normal carriers of these organisms and of other pathogens, etiological classification of these acute throat infections cannot be definitely made at present.

For clinical purposes, then, although not for epidemiological ones, it seems desirable to use the term streptococcus sore-throat to include streptococcus infections of the tonsils and adjacent tissues characterized chiefly by marked congestion, swelling and pseudomembrane. It must be remembered that milder forms, classed clinically as pharyngitis, follicular and lacunar tonsillitis, etc., having important differences in appearance, course and complications, may be due to the same cause and capable of transmitting the infection to others in the severe form.

Etiology.—Hemolytic streptococci, virulent for rabbits and mice, are found in cases of streptococcus sore-throat, both of epidemic and endemic type. Identification of one strain as the cause of either the epidemic or endemic forms has not been definitely settled. It is probable from the work of Smith and Brown, Davis and Capps, Mathers and others that the streptococci in milk-borne epidemics are of human origin rather than bovine. The cows become infected from human sources and the infected udder serves as a ready means of dissemination of enormous numbers of the organisms through the milk.

Predisposing Factors—*Season.*—Septic sore-throat occurs more frequently in the cold months of winter and spring. Epidemic outbreaks have usually appeared at these times.

Age.—No age is immune but infancy seems to be relatively free. In the Cambridge epidemic and in four epidemics cited by Winslow the age periods were:

AGE DISTRIBUTION OF SEPTIC SORE-THROAT

<table>
<tr><th>Epidemic</th><th>Per Cent under 11</th><th>Per Cent between 11 and 20</th><th>Per Cent between 21 and 30</th><th>Per Cent between 31 and 40</th><th>Per Cent between 41 and 50</th><th>Per Cent between 51 and 60</th><th>Per Cent over 60</th><th>Total</th></tr>
<tr><td>Westchester .....</td><td>30.3</td><td>14.1</td><td>18.6</td><td>17.4</td><td>9.7</td><td>4.2</td><td>5.4</td><td>402</td></tr>
<tr><td>Cambridge ......</td><td>11.6</td><td>11.8</td><td colspan="2">44.5</td><td colspan="2">23</td><td>9</td><td>467</td></tr>
</table>

Sex.—In the epidemic form due to infected milk, females predominate in from 57 per cent to 70 per cent, probably due to the greater use of milk, as extensive epidemics have occurred in boys' schools when supplied with infected milk.

Local Conditions.—The lymphoid structures, as the tonsils, are distinctly more liable to attack than other throat tissues as in diphtheria. In tonsillectomized cases, septic sore-throat has been less frequent in my observation and when it occurs is more likely to involve the pharyngeal wall rather than the fauces.

Other Diseases.—Streptococcus infections are strikingly associated with several other diseases, but especially with scarlet fever, measles and smallpox. The former is one of the greatest known predisposing causes. Measles, strange to say, shows a markedly less tendency to streptococcus sore-throat, although there is a striking susceptibility to pulmonary and middle-ear infections. Faucial diphtheria of the phlegmonous type in the opinion of some writers is considered always as a mixed infection with streptococci. While it is undoubtedly true that diphtheria leads to secondary streptococcus infection, such as otitis media and cervical adenitis, the phlegmonous (so-called septic) diphtheria of our experience does not justify this view. This opinion is based on the difference in the local inflammation, the nearly uniform rapid subsidence under antitoxin, the absence of abscess and other complications frequent in streptococcus infections and the great proneness to the characteristic late toxic degenerations, such as paralysis.

Relation of Streptococci and Scarlet Fever.—The extraordinary association of streptococcus sore-throat and scarlet fever and the similarity of the complications of these two diseases have led some observers to maintain that they are due to the same cause. In epidemics of milk-borne streptococcus sore-throat, a few cases with eruption simulating scarlet fever have occurred. However, large milk-borne epidemics (1909) of scarlet fever have occurred in Boston in which no great prevalence of streptococcus sore-throat has been seen, except complicating scarlet fever cases; and other epidemics (1911) have occurred of streptococcus sore-throat in which no striking increase of scarlet fever has appeared. In one epidemic (Canton, 1913), on the other hand, there appeared in the same milk supply and often in the same household coincident cases of scarlet fever, both complicated and uncomplicated clinically by streptococcus sore-throat, and of streptococcus sore-throat in which evidence of scarlet fever was absent. It is of course clear, as both these diseases are endemic in large cities, that in epidemics of either there are apt to be included a certain number of the other non-epidemic disease. While definite decision of this interesting relation must await more knowledge of the etiology of scarlet fever, the clinical decision, to our mind, must be that they are independent infections.

Immunity.—Little is known of the *natural immunity* to streptococcus sore-throat. Infections of various kinds due to streptococci, however, are extremely common. In milk-borne epidemics a considerable number who have partaken of the milk escape. Capps and Miller reported that of 153 nurses in a hospital supplied with the infected milk 52 per cent developed streptococcus sore-throat; of 252 households in Chicago using this milk, 51 per cent had cases of streptococcus sore-throat; while at Batavia of 50 households 66 per cent had the infection. There is no doubt that the number of organisms securing entrance to the patient's throat in milk-borne epidemics is greater by far than occurs commonly in contact spread.

Acquired immunity seems to be relatively slight, repeated attacks being well known in this as well as in other streptococcus infections such as erysipelas. Koch and Petruschky inoculated a man suffering from a malignant tumor with a streptococcus obtained from erysipelas. He developed a moderately severe attack of ten days' duration. After subsidence, reinoculation produced the same result. This was repeated ten times. Serum of artificially immunized animals contains protective substances for infected animals as shown by Denys, Marchand, Aronson, etc. Such immune serum may protect mice from ten times the fatal dose of streptococcus culture if given at the same time, but requires much larger doses if it is delayed four to six hours after infection and the results are much less constant. Protection is more complete against the strain used for immunization, but protection may also occur against other strains.

Epidemiology.—Epidemics of streptococcus sore-throat have been of frequent occurrence in England. Eighteen epidemics (1888-1904) were reported by Savage and their relation to infected milk supply was shown.

The first known epidemic in this country occurred in Boston in May, 1911, in which over 1,000 cases occurred. Similar epidemics have since occurred in several places. These epidemics are characterized by an explosive nature, most of the cases occurring in one week, by great virulence and by being traced to the milk supply. Virulent, hemolytic streptococci have been isolated from the throats of patients, from the udders of cows supplying the milk, from the mixed milk and from the throats of milkers or farmers. These organisms seem to be identical. Smith and Brown believe the streptococci are of human origin transplanted to the cow by milkers, and Davis and Capps have produced experimental mastitis in cows with streptococci of human origin. They found that scarification of the teat and the application of streptococcus cultures or that injection of streptococcus cultures into the milk ducts were necessary to produce infection. They draw attention to the important fact that gross evidence of mastitis or garget might be absent even when virulent streptococci and pus were discharged from the infected udder. They demonstrated the persistence of streptococci in the udder over four weeks. Mathers has also produced mastitis in cows, with hemolytic streptococci both virulent and non-virulent for rabbits, and shown the persistence of virulent organisms in milk from the infected quarter for long periods, that is, two hundred fifteen days. The streptococcus commonly found in milk, Streptococcus lacticus, is not virulent for rabbits and probably not for man (Davis, Smith, etc.). The amount of milk necessary for infection

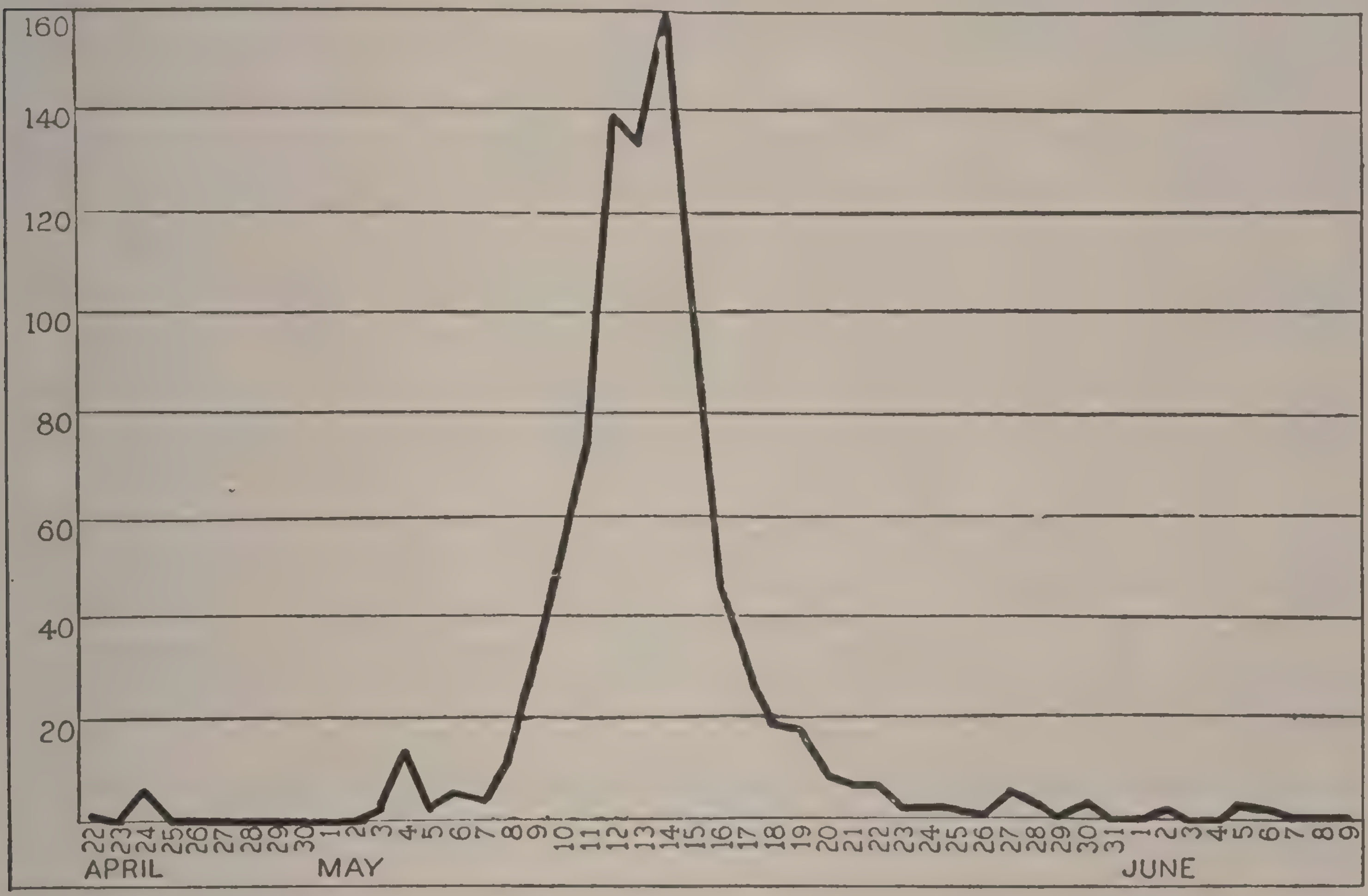

Fig. 1.—Occurrence of Cases in the Greater Boston Epidemic. (Winslow.)

of man may be very small. In one of the Boston cases, the only milk from the infected source was cream sufficient for one cup of coffee.

Contact Spread.—The appearance in milk-borne epidemics of subsequent cases by contact has been very slight but it is not rare in the endemic form. Even in milk-borne epidemics evidence of prosodemic spread has been clearly present as in the Marlboro and Hudson epidemics and in the Westchester County epidemic, as shown by Winslow. In the Batavia epidemic, Capps and Davis also demonstrated that contact played some part. There is a possibility that the infrequency of secondary attacks in the milk-borne epidemics may be due to immunity as demonstrated by their escaping the milk infection. Keegan reported a small but serious contact epidemic in a hospital.

Streptococcus Carriers.—Streptococci are frequently found in apparently normal throats. Park and Williams found 83 carriers in 100 healthy persons and Pilot and Davis found hemolytic streptococci in the depths of the tonsil crypts even when absent from the surface. Hemolytic streptococci were found in 61 per cent in swabs from the tonsils and in 97 per cent from the same tonsils after excision. The organisms were less frequent in the throats of tonsillectomized persons than in those with tonsils. Just how important, if at all, these normal carriers are in the prevalence of streptococcus sore-throat cannot be said until the classification and pathogenicity of the streptococci are better known and some means of determining immunity is secured. In army camps, during the war, it was found by numerous observers that close association of patients with streptococcus carriers led frequently to the carrier condition developing in these and that measles occurring in streptococcus carriers was much more prone to complications. At present it seems not improbable that reduced resistance locally or generally from exposure, metabolic disturbances or from other diseases may allow streptococci present in the throat to become harmful to the patient. And yet it is generally found in other carrier diseases that immunity to the organism is the rule. Streptococci were found in an epidemic by Sharp, Norton and Gordon to persist for eight weeks, or more, in 5 of 8 cases studied. In these cases there was a persistent redness of the throat in the carriers which is in agreement with observations of carriers of scarlet fever.

Incubation.—In epidemics the incubation has been usually short, one to two days. In endemic cases it seems to be longer but is often difficult of determination. It is probably from one to seven days.

Symptoms.—The onset is usually abrupt, with chilliness, sore-throat, fever, headache, backache and often vomiting and diarrhea. In the severer forms prostration is very marked and persistent and delirium may occur. The dominance of vomiting and diarrhea with signs of severe toxemia in rare instances may mislead the unwary to overlook the throat infection.

The throat, if seen early, usually shows extensive and brilliant injection of the whole fauces, often with swelling of uvula, pillars and tonsils. Thin membrane or spots of exudate may occur on tonsils or pillars or uvula. The swelling and pseudomembrane often rapidly increase so that in two or three days the membrane may cover the pillars, uvula and palate as well as the tonsils and produce great difficulty in swallowing and even in breathing. The false membrane varies greatly in appearance. It is often more white than other pseudomembranes but may be yellowish or blackish. It is often friable and easily swept off, but in the more extensive cases its adherence is as great as in diphtheria. The edge tends to shade down into the surrounding tissue and often shows an irregular outline. Necrosis and loss of tissue may be evident. The injection surrounding the membrane is practically invariably intense and extensive.

There is very frequently (50 to 90 per cent) involvement of the lymph-nodes at angles of jaw varying from small discrete masses to large tumors from two to three inches in diameter with marked periglandular induration and tenderness. The swelling is usually more tender and firm with more definite limitation to the lymph-nodes than is seen usually in the severe diphtheria cases. It is sometimes confused with parotitis.

Course.—The infection tends to run its course in from a few days to two weeks. In favorable cases spontaneous improvement is as rapid and satisfactory as seen in diphtheria under antitoxin treatment. The membrane rapidly clears, the swelling subsides, the temperature drops by lysis. In unfavorable cases, the infection persists with high and often irregular fever and with great swelling and extensive membrane; signs of toxemia are marked; there is great restlessness; the infection may spread to various other tissues as noted in complications; there is rapid loss of weight, and death may occur, usually with septicemia or pyemia. Extensive ulceration may occur involving tonsils, pillars, uvula or palate, but on subsiding these lesions may heal with surprising completeness. In some cases, perforation of the palate may be left. Relapse may occur in a week or ten days and the patient pass through another inflammation. After subsidence of the infection, there may be weakness, pallor or listlessness for several weeks.

Blood.—Polymorphonuclear leukocytosis, 10,000 to 40,000, usually occurs, although in some of the severe cases no leukocytosis appears. There may be at times a primary leukopenia. Loss of hemoglobin may be marked during the acute stage.

Eruptions.—Toxic eruptions occur in a small percentage. They may appear as petechial hemorrhages, sometimes profuse but more commonly on the extremities. In some of the embolic type, local areas of necrosis occur. Irregular, macular rashes, usually coarse and often transient, occur on the extremities and less frequently on the trunk, due apparently to toxic effect on the vasomotor system. Scarlatiniform eruptions were reported by Darling in 1 per cent. There is always the possibility of incidental cases of scarlet fever being included in such a group. Erysipelas is a well-known complication.

Complications.—Complications are frequent and often serious. Infection may spread along the surface of the mucous membrane as to the nasopharynx, nose or larynx or into the sinuses. It may follow the lymphatics into the lymph-nodes or spread directly into the tissue of the neck, producing cellulitis. It may gain access to the blood from various sites leading to pyemia or septicemia.

Septic Rhinitis.—Extensive membrane may occur in the nares or nasopharynx with nasal obstruction and profuse mucopurulent discharge.

Otitis Media.—This is very apt to occur in these cases. Inflammation is rapid, perforating the drum unless incised, and is attended by a purulent discharge which may be thin or thick. Extensive destruction of the bony tissues may occur and complete deafness may result from otitis interna.

Mastoiditis.—This is a frequent sequel of otitis media. While the usual signs such as postaural tenderness and swelling are frequent, in some cases with a thick external wall the mastoid involvement may be obscure, high fever and signs of intoxication, not otherwise explained, only suggesting this complication.

Lateral Sinus Thrombosis and Abscess.—These may result especially in these "blind" cases of mastoiditis or where prompt mastoid drainage is not secured by operation.

Sinusitis.—Involvement of the nasal sinuses in the septic rhinitis cases is not infrequent but is often obscure. It is probable that it is frequently overlooked unless X-ray or transillumination is used. Ethmoiditis has been more frequently recognized in our cases. This may be shown in marked cases by a swelling and tenderness at the side of the nasal bridge, at the inner canthus of the eye. Rupture of the sinus may occur on the cheek or into the orbit of the eye.

Cervical Adenitis.—This may occur early during the acute faucial inflammation or appear later after the throat has partly or completely cleared. In the severer cases, it is an almost constant complication. Abscess frequently follows especially where there is much periglandular infiltration. The abscess tends to localize and point at the surface, but burrowing may occur, if neglected, along the fasciæ of the neck or even into the mediastinum.

Peritonsillar Abscess.—This may develop but is much less frequent in the cases showing extensive membrane.

Ludwig's Angina.—Rarely a diffuse cellulitis of the neck produces a brawny, tender collar encircling the front of the neck. Swallowing and breathing may be difficult. Edema of the larynx may occur and cause rapid asphyxia unless tracheotomy is done.

Laryngitis.—Streptococcus infection of the larynx may occur, producing rapid stenosis simulating diphtheria. Swelling and destruction is often marked and chondritis and perichondritis of the laryngeal cartilages and peritracheal abscess are apt to occur.

Nephritis.—In the endemic cases, nephritis is not common although in the epidemic cases it has occurred in from 0.5 to 3 per cent.

Arthritis.—Simple or rheumatic arthritis is a fairly frequent complication, occurring in from 5 to 10 per cent. It is, however, less frequent than in the milder forms of tonsillitis. It is not distinguishable from true rheumatic arthritis. *Septic arthritis* may occur with or without other types of pyemia. The rapid distention of the joint cavity with fluid (pus) in contradistinction to the greater periarthritic involvement of the rheumatic cases is suggestive as are also the high fever and other evidences of septicemia.

Erysipelas.—This has been a striking complication in the epidemic forms and occasionally in the endemic. It appears either at the nostril or about the nose or at the mouth. It may start at wounds, such as burns, scratches. In two cases I have seen it appear on the ear, apparently following up the eustachian tube. In one case myringitis preceded its appearance in the canal and concha from which it spread over the face. The drum subsided rapidly without rupture or other evidences of otitis media. When the erysipelatous inflammation involves the mucous membranes before appearing on the skin, it is not readily recognized as such.

Endocarditis.—Benign endocarditis is apparently less common than in the milder forms of tonsillitis of the follicular type, occurring in from 1 to 2 per cent. *Septic endocarditis* occasionally occurs. *Phlebitis* may occur chiefly in the legs. Gangrene and embolism are rare.

Meningitis.—This may occur by extension from a mastoiditis or sinusitis or as part of a septicemia. Infection may follow through the cribriform plate from a septic rhinitis. Brain abscess is rare.

Hemorrhage.—Nasal hemorrhage may occur and rarely hemorrhage from ulceration of the throat. Erosion of the deep vessels in the neck has resulted rarely from cervical abscess.

Bronchopneumonia.—This is one of the most serious complications, especially in younger children and the aged. *Empyema* is apt to follow. *Pleurisy* may be primary or secondary to pneumonia.

Peritonitis.—In the Boston epidemic and also in subsequent ones, an idiopathic peritonitis showing pure cultures of streptococcus occurred and was invariably fatal.

Osteomyelitis.—Osteomyelitis is rare.

Septicemia.—Septicemia with or without definite pyemia is apt to be present in the fatal cases.

The frequency of complications, as collected from series of cases in the Cambridge epidemic by Darling, the Westchester County epidemic by Winslow, and in the Chicago epidemic by Capps and Davis are shown in the following table:

FREQUENCY OF COMPLICATIONS

Complication	Cambridge Per Cent.	Westchester Per Cent.	Chicago Per Cent.
Cervical Adenitis	....	50	56
Cervical Abscess	4.5	..	4.6
Peritonsillar Abscess	4.5	12	2.5
Otitis Media	0.7	8	3
Mastoiditis	0.19	..	...
Arthritis non-suppurative	7.2	11	6
Endocarditis	1.3	0.4	2
Pericarditis	0.37	..	...
Myocarditis	0.119	..	...
Laryngitis	0.94	..	...
Bronchopneumonia	2	..	1.6
Empyema	0.56	..	...
Pleurisy	1.5	..	0.15
Meningitis	0.19	..	...
Phlebitis	0.37	..	...
Nephritis	1.1	3	1
Erysipelas	....	2	...
Relapse	....	7	...
Peritonitis	1.5	..	...
Total number of cases	527	905	521

Diagnosis.—The diagnosis is often difficult and not infrequently impossible at the first visit. The chief points are: (1) a marked toxic reaction, such as fever, prostration and malaise; (2) the character of the pseudomembrane and the extent and type of redness; and (3) cervical adenitis.

Diphtheria.—Diphtheria is less apt to show a severe constitutional reaction and has a much less intense and extensive redness about the membrane in typical cases. The diphtherial membrane is more apt to be raised or sharply defined, more regular in outline and typically more difficult to remove. The difficulty of certainly differentiating diphtheria in these cases and the grave danger of delaying antitoxin treatment in diphtheria of this type make it excellent practice to administer antitoxin at once.

Scarlet Fever.—Scarlet fever should never be overlooked in cases diagnosed as septic sore-throat. The presence of a rash of the scarlatinal type and distribution may always be accepted in cases of septic sore-throat as justifying the diagnosis of scarlet fever. Differences of opinion regarding septic rashes and scarlet fever eruptions cannot be avoided until the etiology is known. A well-marked strawberry tongue is strongly suggestive. In cases of doubt, it is better to isolate as scarlet fever.

Peritonsillar Abscess.—Peritonsillar abscess is arbitrarily to be distinguished by the less striking involvement of the superficial layers, the infection being deeper in the tissues. It is probable that peritonsillar abscess is due to the same streptococcus and is, therefore, like follicular tonsillitis, one of the clinical forms of this infection.

Vincent's Angina.—This should not cause confusion as here the ulceromembrane is not attended by the marked active inflammation seen in septic sore-throat. The absence of high fever and constitutional symptoms, the slower longer course and the presence of the B. fusiformis and S. vincenti make the differentiation easy.

The appearance of any of the infections noted among the complications should direct attention to the possibility of the throat as the primary focus even if the patient has failed to emphasize the point.

Prognosis.—Prognosis varies with the severity of the constitutional symptoms and the extent of the inflammation. Delirium or stupor, profuse nasal discharge, extensive membrane and swelling of the throat and induration of the neck produce obviously a situation of great danger. The development of pneumonia or septicopyemia is, of course, of great gravity although rarely even the latter recovers. The mortality varies usually from 2 to 5 per cent. In the Greater Boston series, it was about 5 per cent; in Chicago 3.6 per cent. The possibility of permanent disability from involvement of ears, joints, heart or rarely kidney should be kept in mind.

TREATMENT

Specific Treatment.—Direct treatment has been attempted by means of antistreptococcus serum. In our cases, improvement of marked degree has rarely followed its use. Possible variation in the strains of streptococci may be such that antibodies for the desired strain may be absent. Animal experiments, while showing the protective power of serums, have failed to demonstrate curative effects in well-advanced infections. Polyvalent serum, if obtainable, should be used as of possible benefit; but it is unsafe to prophesy a cure.

Vaccines.—Various results have been reported from streptococcus vaccines. Here, as in the serum treatment, the stock vaccine may be of different strain from that of the infection. Progress of the disease is so rapid that it is not probable that benefits may reasonably be expected even from autogenous vaccine therapy.

Local Treatment.—The number of local applications advocated for streptococcus sore-throats is legion. My own experience does not indicate benefit from chemical treatment locally. In most instances, infection is too deep in the tissue for marked local action of bactericides. The striking benefit from strong silver nitrate solution, applied as advocated by Ballinger in tonsillitis, has not been found in the more diffuse infection of streptococcus sore-throat, and often the inflammation is aggravated as is shown if application is unilateral. Hydrogen peroxid as a spray or gargle may aid the disappearance of the membrane and may be of some value.

The most valuable local treatment apparently is heat, applied best as an irrigation, in large quantities—from two to three quarts being used. The pressure should be as little as possible to reach the affected parts and fine nozzles should be avoided.

Hypertonic solutions often give relief and the use of a hot hypertonic solution of 20 per cent glucose is one of the best. In small children and others who will not coöperate, irrigation cannot readily or safely be used. Gagging and choking is likely to increase the danger of otitis media. Protective treatment of the mucous membranes by purified petroleum oil, such as albolene, is often helpful and it may be used as a spray to the throat and nose or by dropper.

General Treatment.—The factors which aid the patient in developing resistance to such infection are not thoroughly known. There is some clinical evidence that the following points are of value:

Fresh Air.—Keeping the patient in the open air seems to have distinct value. There is less restlessness, more sleep, better color and appearance and better appetite under this condition. Cold, as in winter, is no contraindication, although it may make the supervision more difficult.

Sunlight.—There is a suggestion that sunlight has a beneficial action in aiding these patients in the fight against infection. The patient should be gradually accustomed to the light treatment by short and increasing exposure.

Fluids.—A large fluid intake is indicated. In cases which do not take water by mouth it may be given by rectum or subcutaneously as a 5 per cent glucose solution.

Nutrition.—It is very difficult to prevent rapid loss of weight; in fact rapid loss is apparently not incompatible with ability to conquer the infection. At present, it seems wise not to overemphasize a caloric or protein balance, but if possible to give as near this as can be readily done. The use of sugars and fruit juices is helpful in securing readily available energy and milk is usually best suited as a source of protein.

Sleep.—To secure sufficient sleep should not be left to chance. Friends of such patients, on account of the serious condition, restlessness, etc., often expect almost constant attention to the patient. Treatment of all kinds must be planned to allow as much sleep as possible, as often this is more valuable than the procedure which interrupts it.

Drugs.—The salicylates may be of value to relieve headache and pain. Their possible irritating action on the kidney, however, should not be forgotten. Hypnotics, such as allonal, may help. Cold applications to neck and head, cool sponging and alcohol rubs are often conducive to the patient's comfort. Narcotics should be used only when other means fail. Digitalis or caffein may be used if the circulation is poor. Alcohol has been of little value from our observation.

The difficulty of excluding diphtheria in these cases, especially at the beginning, should never be lost sight of. We make it an almost constant rule to administer antitoxin to all such cases at once unless convinced that diphtheria may be excluded. The same dosage as for diphtheria, of course, should be used. There is a very common belief that diphtheria antitoxin benefits the streptococcus cases on account of the rapid improvement which often follows. Antitoxin, however, often entirely fails to stop or modify the disease and it is possible that the apparent benefit is coincidental.

Treatment of Complications.—This constitutes an important part of the problem in these cases.

Cervical Adenitis; Cellulitis.—Local application of ice collars or cold compresses in the early stages are helpful, but heat is usually more beneficial after the first three days. That poultices increase the probability of abscess has not seemed to be borne out in our wards, but they undoubtedly hasten the process. In the absence of spreading, incision may be delayed until the abscess is well localized. Incision should be made in the neck folds to avoid scarring.

Otitis Media.—Frequent inspection of the drum and prompt thorough incision on the appearance of bulging are essential. Both the dry treatment by means of sterile, dry wicks frequently changed and warm irrigations of bland solutions, such as boric acid, are used. Our experience favors the latter.

Mastoiditis.—Mastoiditis should be kept constantly in mind. Tenderness and edema over the mastoid process and bulging of the canal wall usually indicate operation. Continued fever, especially if high, and aural discharge, without other symptoms, may call for careful consideration of the mastoid operation.

Sinusitis.—Sinusitis often tends toward rapid recovery, especially in children, but operation may be required. In some cases, chronic sinusitis may result.

Streptococcus Arthritis.—Early incisions of joints on the appearance of pus are important. The best results have followed the method of Cotton of incision, thorough washing out of the cavity and closure of the wound without drainage. Immobilization is used for a short period.

Prevention.—Milk-borne epidemics may readily be prevented by thorough pasteurization of milk by the holding method. The sudden appearance of many cases should suggest a milk source and data should at once be secured on this point. All milk and cream should be boiled at home or pasteurized before use, even if pasteurization is done at the dairy since defects may have occurred in their methods. The possibility of ice cream being the means of dissemination should be considered. While this should be sufficient to stop the epidemic, search for the source of the focus on the farms should be instituted. Infections of the udder and on the teats of cows, or of the throats, noses or hands of the milkers should be investigated and these should be excluded from the milk supply. The discovery of mastitis in the cow may require microscopic and cultural study of the milk of each quarter of all the cows. The guarding of the milk supply by attention to the health of milkers, especially as to acute respiratory infections, to cleanliness in milking, and to sterilization of utensils is obvious, but not always possible to secure.

Prevention of the endemic form is obviously difficult. The difficulty of clinical and even of bacteriological diagnosis of all the cases, as well as the probable importance and frequency of carriers, makes effective

Epidemics in the United States

Place	Year	Approximate Number of Cases	Reported by
Boston	1911	1043	Winslow. Journ. Infect. Dis., x, 73, 1912.
Baltimore	1912	1000	Frost. U. S. Pub. Health Rep., ii, 419, 1912.
Chicago	1912	10,000	Capps and Miller. Journ. Am. Med. Ass., lviii, 1848, 1912.
Boston	1912	227	Coues. Am. Journ. Pub. Health, ii, 419, 1912.
Concord, N. H.	1913	1000	Mann. Journ. Infect. Dis., xii, 481, 1913.
Jacksonville, Ill.	1913	348	Capps and Davis. Arch. Int. Med., xiv, 651, 1914.
Cortland and Homer, N. Y.	1914	669	North, White and Avery. Journ. Infect. Dis., xiv, 124, 1914.
Wakefield and Stoneham, Mass.	1914	1000	Morse. Am. Journ. Pub. Health, iv, 506, 1914.
Middlebury, Vt.	1914		Eddy. Bull. Vermont State Board of Health, xiv, 25, 1914.
Rockville Center, N. Y.	1914		Overton, Krumwiede and Jacques. Bull. N. Y. State Health Dept., ix, 230, 1914.
Westchester Co., N. Y.	1915	905	Winslow and Hubbard. Journ. Infect. Dis., xviii, 105, 1916.
Galesville, Wis.	1917	325	Hemka and Thompson. Journ. Am. Med. Ass., lxviii, 1307, 1917.
Dorchester, Mass.	1917	227	Smillie. Journ. Infect. Dis., xx, 49, 1917.

measures almost impossible. The well-known precautions to guard against the dissemination of the nose and throat secretions are important. Education of the individual to keep all objects which might become infected away from the mouth and nose may aid.

Prevention of rapid spread by prompt recognition and isolation of other acute infectious diseases, particularly of the respiratory tract, and attention to the general health to avoid reduced resistance may aid in the long run. Removal of tonsils, especially if the seat of periodic inflammation, is indicated. Immunization has not yet reached a practical application.

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NOTE: Therapeutic agents appear in black-face type, as **Balneology.**
Subjects other than treatment appear in plain capitals, as ACROMEGALY.
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